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THERAPEUTIC PRODUCTS GUIDANCE

GUIDANCE ON THERAPEUTIC PRODUCT REGISTRATION IN SINGAPORE

TPB-GN-005-001

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ABBREVIATIONS AND ACRONYMS

ACPM	Advisory Committee on Prescription Medicines
ACRA	Accounting and Corporate Regulatory Authority
ACTD	ASEAN Common Technical Document
ACTR	ASEAN Common Technical Requirements
ASEAN	Association of Southeast Asian Nations
ATC	Anatomical Therapeutic Chemical
BA	Bioavailability
BCS	Biopharmaceutics Classification System
BE	Bioequivalence
BP	British Pharmacopoeia
BSE	Bovine Spongiform Encephalopathy
BWP	Blood Working Party
CECA	Comprehensive Economic Cooperation Agreement
CEP	Certificate of Suitability (Ph. Eur. monograph)
CHMP	Committee for Medicinal Products for Human Use (formerly Committee for Proprietary Medicinal Products) (EU)
CMC	Chemistry, Manufacturing and Controls
CMI	Consumer Medicine Information
CMS	Concerned Member State
COA	Certificate of Analysis
COO	Country of Origin (Finished product manufacturer)
CPP	Certificate of Pharmaceutical Product
CPMP	Committee for Proprietary Medicinal Products
CTD	Common Technical Document
CVMP	Committee for Medicinal Products for Veterinary Use
DCP	Decentralised Procedure
DMF	Drug Master File
DP	Drug Product
DS	Drug Substance
EDQM	European Directorate for the Quality of Medicines
EIR	Establishment Inspection Report
EMA	European Medicines Agency (EU)

FDA	Food and Drug Administration (US)
FTA	Free Trade Agreement
GDA	Generic Drug Application
GSL	General Sale List medicine
GMP	Good Manufacturing Practice
HDPE	High-Density Polyethylene
HIV	Human Immunodeficiency Virus
HPA	Health Products Act
HPRG	Health Products Regulation Group
HSA	Health Sciences Authority (Singapore)
ICH	International Council for Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human use)
INN	International Non-proprietary Names
IPOS	Intellectual Property Office of Singapore
JP	Japanese Pharmacopoeia
MAH	Marketing Authorisation Holder
MAV	Major Variation
MHRA	Medicines and Healthcare Products Regulatory Agency (UK)
MIV	Minor Variation
MRP	Mutual Recognition Procedure
NDA	New Drug Application
NfG	Note for Guidance
OTC	Over-The-Counter
P	Pharmacy-Only Medicine
PD	Pharmacodynamics
PDF	Portable document format
Ph. Eur.	European Pharmacopoeia
PI	Package Insert (Singapore), Product Information
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
PIL	Patient Information Leaflet
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
PMF	Plasma Master File

POM	Prescription-Only Medicine
PRISM	Pharmaceutical Regulatory and Information System
QOS	Quality Overall Summary
RMP	Risk Management Plan
RMS	Reference Member State
SPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
TGA	Therapeutic Goods Administration (Australia)
TSE	Transmissible Spongiform Encephalopathy
URL	Uniform Resource Location
USP	United States Pharmacopeia
WHO	World Health Organisation

CHAPTER A GENERAL OVERVIEW

1 FOREWORD

This guidance document outlines the regulatory processes and requirements for therapeutic product registration and should be read in conjunction with the relevant legislation in Singapore, including:

- Health Products Act (Cap. 122D); and
- Health Product (Therapeutic Products) Regulations 2016.

The Health Products Act (HPA) provides for the legislative basis for regulating the manufacture, import, supply, presentation and advertisement of therapeutic products, one of the health products categories regulated under the *Act*.

1.1 Scope of This Guidance Document

This guidance document describes the procedures and requirements for submitting an application to register a therapeutic product, or to make a variation application to a registered therapeutic product.

Under the First Schedule of the HPA, a therapeutic product means any substance that:

(a) is intended for use by and in humans for a therapeutic, preventive, palliative or diagnostic purpose, including any of the following purposes:

- (i) for preventing, diagnosing, monitoring, treating, curing or alleviating any disease, disorder, ailment, injury, handicap or abnormal physical or mental state, or any symptom thereof;
- (ii) for investigating, modifying, or replacing any physiological process;
- (iii) for influencing, controlling or preventing conception; or
- (iv) for inducing anaesthesia.

(b) has as its constituent any of the following active ingredients:

- (i) any chemical or botanical element, naturally occurring chemical or botanical material or chemical product obtained by chemical change or synthesis;
- (ii) any metabolite from a micro-organism;

- (iii) any macromolecule extracted from an organism; or
- (iv) any substance derived from a biological system, including any of the following:
 - (A) a whole cell or micro-organism, such as a whole virus or bacterium used as a vaccine;
 - (B) a part of a micro-organism, such as a sub-unit vaccine;
 - (C) a plasma-derived product; or
 - (D) a biotechnology-derived substance, such as a protein or polypeptide;
- (c) exerts an inherent effect either pharmacologically, chemically or by other physiological means, leading to its use for a therapeutic preventive, palliative or diagnostic purpose; and
- (d) is not any of the following:
 - (i) a medical device;
 - (ii) any product containing human or animal cell or tissue;
 - (iii) any substance administered to humans with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;
 - (iv) whole blood or any blood component;
 - (v) any Chinese proprietary medicine;
 - (vi) any homoeopathic medicine;
 - (vii) any medicated oil or balm;
 - (viii) any quasi-medicinal product; or
 - (ix) any traditional medicine.

To avoid doubts, items d(v), (vi), (vii), (viii) and (ix), have the same meaning as that under the Medicines Act (Cap. 176) as defined in paragraph 2 of the Medicines (Traditional Medicines, Homoeopathic Medicines & Other Substances) (Exemption) Order.

In making an application for a therapeutic product, applicants should ensure that the submission requirements as specified in this guidance document are duly fulfilled. In a situation where an applicant proposes an alternative to any of the specified requirements, such proposal should be accompanied by scientific justification and should be discussed with HSA prior to making the submission to avoid rejection of the application.

HSA may also request for additional information to supplement the specified submission requirements if deemed necessary for the assessment of the safety, efficacy and quality of the product for which an application is made.

Within this document, the term '*quality*' may be used to describe chemical, pharmaceutical and biological data, while the term '*non-clinical*' may be used to describe preclinical, pharmacological and toxicological data.

Applicants are advised to check [HSA's website](#) for the latest version of this guidance document and other related therapeutic product registration guidelines.

1.2 Therapeutic Product Registration

A therapeutic product registered under the HPA is specific to the product with respect to its:

- proprietary or brand name;
- pharmaceutical formulation;
- pharmaceutical dosage form (i.e. physical presentation) and strength; and
- indication(s) and dosing regimen.

Different formulations, dosage forms and strengths of the same chemical or biologic entity are considered as different products and will require separate registrations for the individual product.

Forensic Classification

Upon satisfying the regulatory requirements for quality, safety and efficacy, a therapeutic product may be registered under one of the following forensic classifications, which determines the level of control for access:

- Prescription-Only Medicine (POM);
- Pharmacy-Only Medicine (P); or
- General Sale List medicine (GSL).

Prescription-Only Medicines (POM) control is required in the following situations:

-
- (a) The product poses a direct¹ or indirect² danger to human health, even when used correctly, if used without medical supervision;
 - (b) The product is frequently and widely used incorrectly and, as a result, is likely to present a direct or indirect danger to human health;
 - (c) The product requires further investigation into its activity and/or side effects; or
 - (d) The product is normally prescribed by a doctor or dentist to be administered parenterally.

The following also needs to be taken into consideration when deciding whether a product should be classified as a POM:

- (a) Whether the product contains a substance which is listed in either the Narcotic Drug Convention or the Psychotropic Substances Convention;
- (b) Whether the product is likely to lead to medicinal abuse or addiction if used incorrectly or to be used for illegal purposes;
- (c) Whether the product contains a substance which, by reason of its novelty or properties, has the potential to fall within point (b) above;
- (d) Whether the product, by reason of its pharmaceutical characteristics, is reserved for treatments which can only be administered in a hospital;
- (e) Whether the product is used in the treatment of conditions which must be diagnosed in a hospital or in an institution with special diagnostic facilities; or
- (f) Whether the product is intended for outpatients but may produce serious side effects, which would require medical supervision throughout the treatment.

Pharmacy-Only Medicines (P) control is required for products that possess characteristics which are not sufficiently critical to warrant POM control but for which the following apply:

- (a) Consultation with a pharmacist is necessary to confirm the appropriate choice of therapy;
- (b) The contraindications, drug interactions, precautions or warnings need reinforcement by a pharmacist or are not easily recognised by the purchaser; or
- (c) Special precaution is needed in the storage and handling of the product.

¹ Direct danger: Adverse reactions for which there is no preventive action or which are serious, severe or of high frequency

² Indirect danger: Masking of an underlying condition that requires medical attention e.g. cancer, heart disease

General Sale List Medicines (GSL) control is sufficient in the following situations:

- (a) The product is reasonably safe and can be sold or supplied without the need for supervision by a registered doctor, dentist or pharmacist;
- (b) The contraindications, drug interactions, precautions and warnings are easily recognised by the consumer; and
- (c) The hazard to health, the risk of misuse, the risk of misdiagnosis, or the need to take special precaution in the storage and handling the product is small.

2 APPLICANT RESPONSIBILITIES

The applicant of a product registration refers to the local company that is applying for the product registration. The applicant company may authorise officers, permanent employees, or designated external parties, all of whom are referred to as the “applicant representative”, to submit the application for product registration in Singapore.

According to Section 30(10) of the HPA, an applicant, in making an application for the registration of a therapeutic product, must ensure that all information contained in the application is truthful and is not misleading. An applicant must inform HSA of any emerging information that may affect the benefit-versus-risk assessment of the therapeutic product to which the application relates, as soon as the applicant becomes aware of such information.

The applicant is responsible for submitting the application and all the accompanying supporting documents (including but not limited to the dossier, responses to HSA’s queries and commitment letters).

HSA may require a statutory declaration by the applicant verifying any information contain in or relating to the application.

3 WHETHER A THERAPEUTIC PRODUCT IS SUBJECT TO PATENT

An applicant for registration of a therapeutic product is required to make a declaration on whether the therapeutic product for which registration is sought is subject to a

subsisting patent, pursuant to Regulation 23 of the Health Products (Therapeutic Products) Regulations, hereafter referred to as the *Regulations*.

The declaration must be made in the form specified in Appendix 1 – Form 1 of this guidance document and furnished at the time of making the application, as well as at any other such time as HSA may require. A second declaration is required prior to the grant of registration.

A registration application may be declared as one of the following categories:

- Category A1: where no patent is in force in respect of the therapeutic product to which the application relates;
- Category A2: where a patent is in force in respect of the therapeutic product to which the application relates and the applicant is either the proprietor of the patent, or if the applicant is not the proprietor of the patent, the proprietor has consented to or acquiesced in the grant of the registration;
- Category A3: where a patent is in force in respect of the therapeutic product to which the application relates, the applicant is not the proprietor of the patent and the proprietor has not consented to or acquiesced in the grant of the registration, and the applicant is requesting for the grant of registration after the patent expires. Such an application may not be made earlier than 18 months before the patent expires;
- Category B: where a patent is in force in respect of the therapeutic product to which the application relates, the applicant is not the proprietor of the patent and the proprietor has not consented to or acquiesced in the grant of the registration, and in the applicant's opinion and to the best of his belief the patent is invalid or will not be infringed by the performing of the act for which the registration is sought.

The person who is making the declaration must be duly authorised to act on behalf of the applicant. The authorised person is ordinarily an officer of the company such as a director, the company secretary as registered with ACRA, or equivalent. Evidence of such authorisation of such a person by the applicant must accompany the declaration at the point of submission. Examples of evidence of authorisation include a resolution of board of directors, a resolution of a general meeting of the company, or an extract of the relevant portion of the company's articles of association. Declaration forms must

bear the original signatures of the authorised person and the company stamp of the applicant.

Where an application is declared as a Category B application, HSA will require the applicant to serve a notice to the proprietor of the patent in the form specified in Annex 1 – Form 2 of this guidance document. An applicant may also be required to serve a notice where HSA considers it appropriate.

The information contained in this section serves solely as guidance on the requirement for submission of declaration on patent status for the purpose of product registration. HSA does not provide advice on the category under which an application should be declared or whether a therapeutic product is subject to a subsisting patent. An applicant requiring such assistance should seek appropriate legal advice.

4 PROTECTION OF CONFIDENTIAL SUPPORTING INFORMATION AND REGISTRATION EXCLUSIVITY

Regulation 26 and 29 of the *Regulations* provide for protection of confidential supporting information relating to innovative therapeutic product applications and exclusivity of safety and efficacy data, respectively.

Confidential information received in support of the registration of an innovative therapeutic product is protected for a period of 5 years from the date of receipt, during which HSA will not use the information to determine whether to grant any other registration applications. In this regard, confidential supporting information refers to trade secrets and information that has commercial value that would be, or would likely to be, diminished by disclosure.

A 5-year period of exclusivity is granted for a therapeutic product for which safety and efficacy data has been generated in support of its registration. During the exclusivity period, a subsequent similar therapeutic product will not be able to rely on such data generated for the earlier therapeutic product to obtain registration.

CHAPTER B REGISTRATION PROCESS

A company seeking to market a therapeutic product in Singapore must obtain marketing approval from HSA through making an application for product registration. The registration process involves a series of steps, as shown in Figure 1.

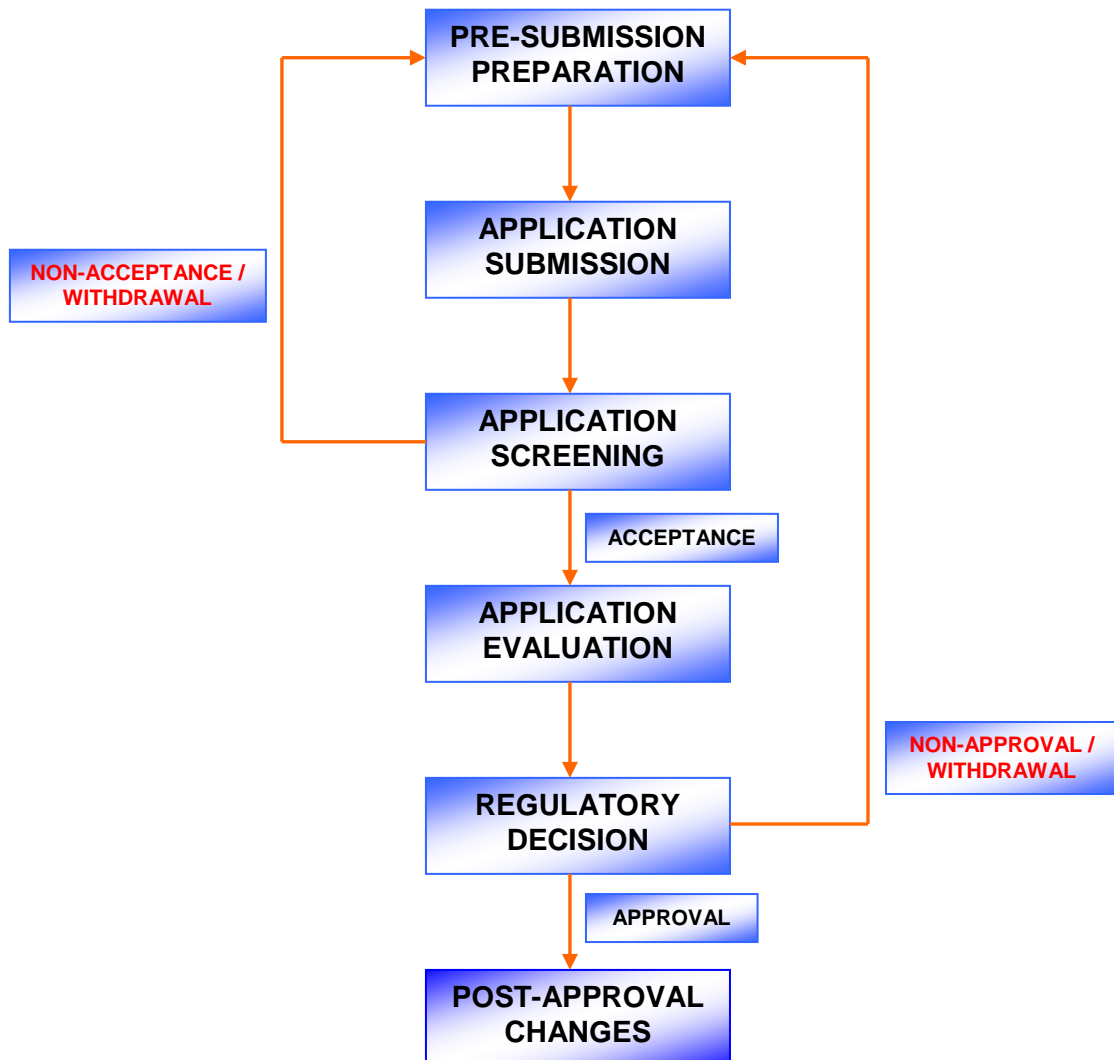


Figure 1 Registration Process for a Therapeutic Product

5 PRE-SUBMISSION PREPARATION

The following are important considerations for an application to register a therapeutic product:

- (a) Knowing which type of application to apply for;
- (b) Knowing which evaluation route to choose; and
- (c) Arranging for a pre-submission consultation with HSA for advice, if required.

5.1 Product Types

A therapeutic product could contain either chemical or biological entity(ies) as the active ingredient(s).

A chemical entity refers to any chemical element, naturally occurring chemical material or chemical product obtained by chemical change or synthesis (including macromolecules produced by chemical synthesis, such as peptides/oligonucleotides), or any metabolites from a micro-organism (such as antibiotics).

A biological entity refers to any macromolecule extracted from an organism (such as proteins, nucleic acids, proteoglycans, cytokines and growth factors), or any substance derived from a biological system, including any of the following:

- (a) a whole cell or micro-organism, such as a whole virus or bacterium used as a vaccine;
- (b) a part of a micro-organism, such as a sub-unit vaccine;
- (c) a plasma-derived product; or
- (d) a biotechnology-derived substance, such as a protein or polypeptide.

5.2 Application Types

In applying for a new product registration for a therapeutic product in Singapore, there are two categories of applications – a new drug application (NDA) and a generic drug application (GDA):

NDA New Drug Application

NDA-1: For the first strength of a product containing a new³ chemical or biological entity.

NDA-2: (a) For the first strength of a product

- (i) containing a new combination of registered chemical or biological entities;
 - (ii) containing registered chemical or biological entity(ies) in a new dosage form (e.g. tablets, capsules, injectables), new presentation (e.g. single-dose vials, multi-dose vials, pre-filled syringe) or new formulation (e.g. preservative-free);
 - (iii) containing registered chemical or biological entity(ies) for use by a new route of administration; or,
 - (iv) containing registered chemical or biological entity(ies) for new indication(s), dosage recommendation(s) and/or patient population(s).
- (b) For products that do not fall under the requirements for NDA-1, NDA-3 or GDA.

NDA-3: For subsequent strength(s) of a product that has been registered or has been submitted as an NDA-1 or NDA-2. The product name, dosage form, indication, dosing regimen and patient population should be the same as that for the NDA-1 or NDA-2.

³ i.e. not a currently registered entity in Singapore. Currently registered therapeutic products can be found in the [Register of Therapeutic Products](http://www.hsa.gov.sg) at www.hsa.gov.sg.

GDA Generic Drug Application

A generic drug application applies to a therapeutic product that contains one or more chemical entities, and that is essentially the **same** with a current registered product with respect to its qualitative and quantitative composition of active ingredients, pharmaceutical dosage form and clinical indication.

Follow-on biologic products (also known as biosimilar products) are not eligible for a GDA and are required to be submitted via a NDA.

GDA-1: For the first strength of a generic chemical product.

GDA-2: For subsequent strength(s) of the generic chemical product that has been registered or submitted as GDA-1. The product name and dosage form should be the same as that for the GDA-1.

In cases where multiple strengths of a generic product are submitted together, the strength of the product used in the BE study is considered as GDA-1. The remaining strength(s) should be submitted as GDA-2.

Figure 2 is a schematic diagram illustrating the various types of applications:

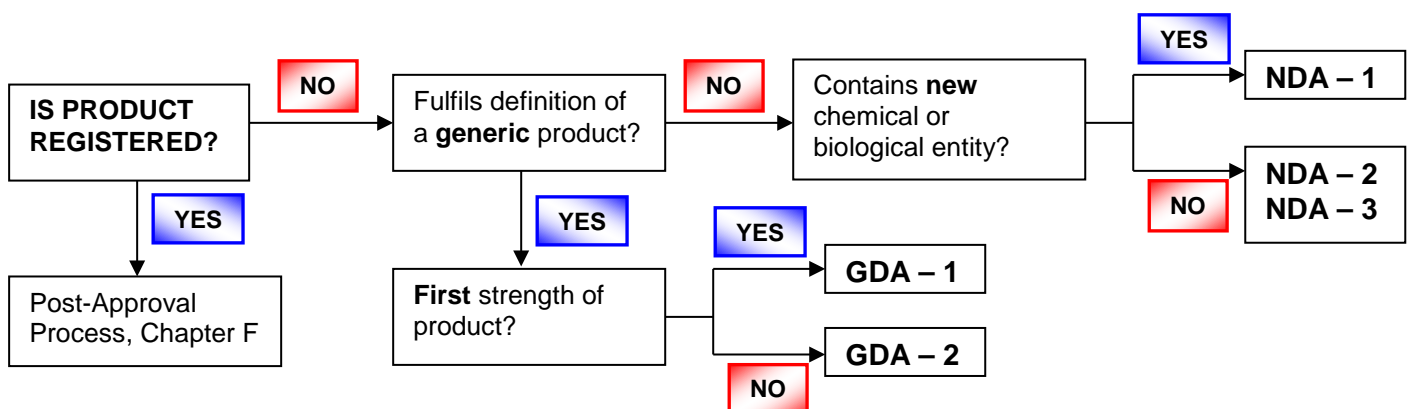


Figure 2 Schematic Diagram of Application Routes for Drug Registration

If there are doubts regarding which is the appropriate application type to choose, applicants are encouraged to consult HSA via the [online feedback form](#) on the HSA website prior to the submission of an application.

5.3 Evaluation Routes

There are four types of evaluation routes for registering a new therapeutic product:

- Full route: Applies to any new product that has not been approved by any drug regulatory agency at the time of application submission to HSA.
- Abridged route: Applies to any new or generic product that has been evaluated and approved by at least one drug regulatory agency.
- Verification route: Applies to any new or generic product that has been evaluated and approved by HSA's reference drug regulatory agencies, which include EMA⁴, US FDA, Health Canada, TGA and UK MHRA⁵.
- Verification-CECA route: Applies to any generic product manufactured in India which has been evaluated and approved by HSA's reference drug regulatory agencies, which include EMA⁴, US FDA, Health Canada, TGA and UK MHRA⁵.

Applicants should refer to [Chapters C, D](#) and [E](#) for detailed information about the selection of appropriate evaluation routes for NDA, GDA and Biosimilar product applications, respectively.

5.4 Pre-Submission Consultation

Applicants are encouraged to contact HSA prior to the submission of an application if questions arise or clarification is required. There are two methods to contact HSA:

⁴ For products approved via the Centralised Procedure

⁵ For products approved via the national procedure or where MHRA acted as the RMS for the MRP or Decentralised Procedures in Europe

- (a) Pre-submission Enquiry via the [online feedback form](#) on the HSA website; and
- (b) Pre-submission Meeting/ Notification

A Pre-submission meeting is generally advisable if there are uncertainties on the eligibility for an application type, evaluation route, or whether the application dossier adequately fulfils the specified submission requirements. Advice given at pre-submission meetings will be based on information current at the time of the consultation and have no bearing on the eventual outcome of the application concerned.

5.4.1 Pre-Submission Enquiry

An applicant may submit a Pre-Submission Enquiry via the [online feedback form](#) on the HSA website to clarify any matters concerning the application prior to submission. The enquiry type selected should be “Therapeutic Product Registration” to minimise delays in the processing of the enquiry.

5.4.2 Pre-Submission Meeting/ Notification

An applicant may request for a pre-submission meeting if a face-to-face consultation with HSA is necessary to address specific submission issues. The request should be made in writing, stating the purpose, agenda and proposed date and time for the meeting, via the [online feedback form](#) on the HSA website.

The meeting request should be made at least 3 weeks prior to the meeting date, and relevant meeting documents (e.g. presentation slides, briefing documents, etc.) should be provided at least 1 week before the meeting.

A pre-submission meeting is not compulsory for an application filed via the full evaluation route. Nonetheless, the applicant is required to notify HSA at least two months prior to the intended submission date. The notification can be sent via the [online feedback form](#) on the HSA website, and should include information on the product name (if available), active ingredient(s), summaries of the quality, non-clinical and clinical data (e.g. Overviews), planned submissions in other countries, and planned date of submission to HSA.

6 APPLICATION SUBMISSION

The submission of an application comprises two key steps – (i) online submission of the application form via [PRISM](#) and (ii) submission of the technical dossier.

6.1 PRISM Application Form

All applications must be made online via PRISM. Please refer to Appendix 17 *Guideline on PRISM submission* for further details.

6.2 Application Dossier

The technical dossier accompanying the application should be submitted within 2 working days of the PRISM application submission to prevent delays in the processing of the application. **The date of receipt of the actual technical dossier by HSA will be taken as the submission date where the processing time starts.**

Application dossiers should be organised in a CTD format. The CTD provides a common format for the preparation of a well-structured submission dossier. It uses a modular framework described in [ICH Topic M4](#) or the [ASEAN guidelines](#) on the *Common Technical Document for Registration of Pharmaceuticals for Human use: Organisation of the Dossier*. This guidance document should be read in conjunction with the current version of the ICH CTD and the ASEAN CTD (ACTD) guidance documents.

Either the ICH CTD or the ACTD format is acceptable for making a submission to HSA. Table 1 summarises the organisation of the respective format:

Table 1 Format of the ICH CTD and ACTD

Documents	Location in	
	ICH CTD	ACTD
Administrative Documents and Product Information	Module 1	Part I
Common Technical Document Overview and Summaries	Module 2	<i>Incorporated in Parts II, III and IV</i>
Quality documents	Module 3	Part II
Non-clinical documents	Module 4	Part III
Clinical documents	Module 5	Part IV

Application checklists for both ICH CTD and ACTD dossiers are provided in Appendix 2A and 3A, respectively, to guide applicants on the submission requirements and to ensure completeness of the dossier. **Each application must be accompanied by a checklist duly completed by the applicant and attached in PRISM.**

Applicants should note that the CTD format **cannot** be changed once the application is submitted. Any subsequent variation applications for the product should follow the same format.

6.2.1 Submission Requirements

The complete application dossier – i.e. Modules 1 to 5 of the ICH CTD or Parts I to IV of the ACTD – must be submitted in an electronic format.

All documents required under Module 1/Part I must be submitted in softcopy in PRISM. Colour scanned copy of the original documents should be submitted and original hardcopy of documents are not required. However, HSA reserves the rights to request for the submission of the original or certified true copy of the submitted document if there is any doubt that the submitted scanned document is not an accurate reflection of the original document.

Please refer to [section 6.2.3](#) for more information on certifying non-original documents if the original documents cannot be provided.

For Modules 2 to 5/Parts II to IV, applicants can opt to attach the documents either in full into PRISM section 7 (Supporting Attachments) or submit the softcopies (e.g. PDF format) in a CD/DVD.

Submitting a CD or DVD

When submitting a CD/DVD, applicants are encouraged to organise the dossier (i.e. folders and subfolders) according to the CTD format and to include bookmarks in all documents to facilitate the retrieval of documents.

Files containing the below scripts will not be accepted due to cybersecurity reasons:

S/N	Script Type	Extension
1	VB Script	*.vbs, *.vbe, *.vb
2	VBA	*.vba
3	JS Script	*.js, *.jse
4	Windows Script File	*.wsf, *.ws
5	Windows Script Component	*.wsc, *.wsh
6	Powershell	*.ps1, *.ps1xml, *.ps2, *.ps2xml, *.psc1, *.psc2
7	Monad (legacy Powershell)	*.msh, *.msh1, *.msh2, *.mshxml, *.msh1xml, *.msh2xml
8	Windows Shell	*.com
9	Batch	*.bat, *.cmd
10	Python	*.py, *.pyo, *.pyc, *.pyw, *.pys
11	Perl	*.pl, *.pls, *.p
12	Shortcut	*.lnk

The CD/DVD should be properly labelled with the following information:

- PRISM application number;
- PRISM submission date;
- Product name;
- Application type; and
- Contents of the CD/DVD (e.g. Module 2, 3 and 5).

Applicants must ensure the access to the content of CD/DVD. For protected files, password(s) must be provided as appropriate.

Upon acceptance of the application for evaluation, applicants will be notified if additional copies of clinical documents (in CD/DVD) will be required.

6.2.2 Language and Translation

All documents submitted in support of an application to HSA must be in English. For documents in their original language which is not English, a certified translation or a verified translation may be acceptable.

<u>Translation type</u>	<u>Type of Documents</u>	<u>Requirements</u>
Certified Translation	<ul style="list-style-type: none"> ▪ Official certificates issued by the drug regulatory agency of a country ▪ Proof of approval issued by the drug regulatory agency of a country 	<p>Notarisation & Authentication</p> <p><u>(a) Notarisation</u></p> <ul style="list-style-type: none"> ▪ These documents must be notarised by a notary public in country where document is issued. ▪ Details of particulars to be included by notary: <ul style="list-style-type: none"> (i) The name of the notary; (ii) A statement that the notary is duly admitted to practice in the place of issue of the certificate; (iii) The names of the signatories and the capacity in which they have executed the document, whether on their own behalf or in an official or representative capacity; (iv) A statement authenticating the signatures of the parties and, where appropriate, indicating that evidence has been produced to the notary proving the capacity in which they have executed the document; (v) The place and date of issue of the notarial certificate; and

		<p>(vi) The signature and seal of the notary.</p> <p><u>(b) Authentication</u></p> <ul style="list-style-type: none"> ▪ These documents must be authenticated (i.e. the origin of the document is attested to) by one of the following government bodies:- <ul style="list-style-type: none"> (i) The Ministry of Foreign Affairs of the country in which the document was issued; or (ii) The Singapore Embassy/Consulate in the country where the document was issued. <p>Applicants are advised to consult the Singapore Embassy/Consulate in the country where the document originated regarding the local requirements for document legalisation, as these may deviate from the process as outlined in the preceding paragraph.</p>
Verified Translation	<ul style="list-style-type: none"> ▪ Technical documents (e.g. package insert, submission dataset) 	<p>Verification Document</p> <ul style="list-style-type: none"> ▪ A verification document must be provided by the translator of the document into the English language. ▪ The verification document must state that the translation into English is accurate. ▪ Details of particulars to be included in verification document: <ul style="list-style-type: none"> (i) the name of translator; (ii) a statement that he/she is well versed in English and the relevant foreign language; and (iii) a reference to the document being translated.

		Refer to the sample verification document for translator enclosed in Appendix 4.
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6.2.3 Certifying Non-Original Documents

If the softcopy official document (e.g. CPP, GMP certificate, etc.) submitted to HSA in PRISM is not a scan of the original document, the document must be certified prior to submission. A certified true copy certifies that the photocopy presented is a true and accurate copy of the original document. Acceptable certification of documents to support therapeutic product applications to HSA can be done by the Company Director or Company Secretary as registered with ACRA or above, or by an independent authority such as a lawyer, notary public, Commissioner for Oaths/Declarations/Affidavits, Justice of Peace, the original issuer of the document or Embassy/Consulate. A notarised and authenticated copy is the same as a certified true copy.

A certified true copy of approval letters requires certification by the drug regulatory agency that issued the approval letter, a notary public or the Singapore Embassy/Consulate in the country where the approval letter was issued. Certification of approval letters is not required in the event the approval letter is available on the drug regulatory agency's website. In this instance, applicants can provide the internet address (URL) for validation by HSA.

7 APPLICATION SCREENING

Following a submission made via PRISM and the receipt of the application dossier by HSA, the application will be screened to ensure the correctness of the application type and the completeness of the dossier. **The date of receipt of the application dossier (i.e. the technical dossier [e.g. in a CD/DVD] including the application checklist) will be taken as the submission date and the start of the screening timeline.**

During screening, if an application is identified to be more appropriately submitted under a different application type, the applicant will be informed of this change and

the necessary actions to effect this change via an Input Request. More information on the change in application type is described in [section 12.2.1 *Changes to Application Types and Re-routing of Evaluation During Screening*](#).

Applications with the following major deficiencies will not be screened, as screening cannot proceed without the dossier:

- entire dossier sections not submitted (drug substance, drug product, clinical);
- Drug Master File (DMF) not submitted (where applicable); or
- assessment reports not submitted (for verification route).

For such applications, a non-acceptance letter will be issued, following which the PRISM application will be withdrawn by HSA and the dossier will be returned to the applicant.

Applicants are also advised to ensure that the dossier is compiled according to the required format. Failure to adhere to the required CTD format will lead to the non-acceptance of the dossier without screening.

If the dossier submitted is considered to be otherwise incomplete, a screening query letter stating the deficiencies will be issued via PRISM (Input Request) to the applicant. The stop-clock starts when an Input Request is sent and ends upon receipt of a complete and satisfactory response to the query. The total number of Input Requests sent during screening is capped at two. Applicants will be given 20 working days to respond to each Input Request, starting from the date the Input Request is sent.

The application will only be accepted when all deficiencies have been adequately addressed and HSA is satisfied that the dossier is complete for evaluation. An acceptance notice will then be issued via email and the date of acceptance of the application will be taken as the start of the evaluation timeline.

If the applicant fails to address the deficiencies raised during screening, the dossier is considered incomplete for evaluation. A non-acceptance letter will be issued, following which the PRISM application will be withdrawn by HSA and the dossier

will be returned to the applicant. If the application is subsequently re-submitted, it will be processed as a new application.

NOTE: The screening process only checks for the completeness of the application dossier for evaluation. The acceptance of the dossier for evaluation does not denote the adequacy of the data for regulatory approval.

8 APPLICATION EVALUATION

Once the application is accepted, the evaluation stage begins. A query letter may be issued to the applicant if clarification or additional information is required.

The stop-clock starts whenever HSA issues a query letter and ends upon the receipt of a complete and satisfactory response from the applicant.

In situations where the applicant is unable to provide a complete response within the specified timeframe, the applicant should notify HSA as soon as possible after receiving HSA's queries. The application will be considered withdrawn if the applicant fails to observe the specified response deadline.

Applicants are reminded that the submission of additional supporting data not requested by HSA following the acceptance of the application will not be considered, unless prior arrangement with HSA is made for the submission concerned. During the evaluation process, HSA may assess that the application is more suitably evaluated via an alternative route, in which case the application will be re-routed to the appropriate route. Any re-routing of the application will be discussed with the applicant.

HSA may engage external evaluators, experts and advisory committees in the evaluation process, when necessary. These experts include scientists and clinicians from both local and overseas institutions. All external evaluators and experts are bound by agreement to protect the information made available to them. The identity of the external evaluators is kept confidential.

8.1 Evaluation Stages

The progress status of the evaluation is available for certain application types and evaluation routes. Table 2 describes the applicable product applications and the stages of the evaluation:

Table 2 Product Applications Applicable for Notification of Stages During Evaluation

Stages of Notification to Applicant		1 st Stage	2 nd Stage	3 rd Stage	4 th Stage
Application Type	Evaluation Route	Evaluation Status			
		Acceptance for Evaluation	Active Evaluation in Progress	Evaluation at Midway	Completed Evaluation
NDA-1 NDA-2 NDA-3	Full or Abridged	Application is accepted for evaluation. This marks the start of the evaluation timeline.	When active evaluation is in progress for the application	Application is approximately midway through the evaluation (provided that there were no prior stop-clocks which may affect the evaluation progress).	Evaluation is completed for the application.
GDA-1 GDA-2	Abridged, Verification, or Verification-CECA			Applicants can expect to receive the first set of queries from HSA during this stage.	Application is now undergoing the regulatory decision phase, after which a regulatory decision letter [#] will be issued. Applicants can still expect further queries from HSA during this stage.

#The issuance of a regulatory decision letter marks the end of the evaluation timeline for a product application.

Applicants may view the evaluation stage via [Track@PRISM](#). The following screenshots illustrate the change in stages of a pending application:

PZ0951 TRACK@PRISM

Important Notes:
For HSA CRIS registered companies, user has to be authorised with the appropriate access rights via CRIS management module to access the required eservices.

General Search

Enter Transaction No or Application/Submission No for fast and exact matched look-up

Application/Submission Type *

Licence/Permit/Certificate/Listing/Notification/Registration Type *

Enquiry Type *

Transaction No.

Application/Submission No.

Licence/Permit/Certificate/Listing/Notification/Registration No.

Product Name.

Submission Date (dd/mm/yyyy) To

Last Update Date (dd/mm/yyyy) To

Choose these options from the drop-down lists.

Enter PRISM application to view stage of evaluation.

1 Matching Record(s) Page 1 Of 1 [First] | [Previous] | [Next] | [Last]

New Application/Submission for Therapeutic Products - Product Registration (Pending Approval)								
S/No	Application No	Transaction No	Product Name	Application/Submission Status	Submission Date	Last Updated Date	Copy Application	Withdraw Application
1	1600464U	T1600883K	Product ABC	Active Evaluation	05/04/2016	08/04/2016	Copy to draft	Withdraw

The evaluation stage is seen here.

Applicants are also notified via system-generated emails whenever an evaluation stage change occurs.

9 REGULATORY DECISION

A regulatory decision is made following the conclusion of the benefit-risk assessment by HSA based on the data submitted in support of the application. Applicants will be notified in writing of one of the following outcomes:

- Approval – the application satisfies the registration requirements for quality, safety and efficacy;
- Approvable – when the application can be approved subject to adequate response to minor deficiencies;
- Non-approvable – when the application has major deficiencies; or
- Rejection – when the response provided by the applicant fails to address the major deficiencies specified in HSA’s non-approvable decision.

‘Approval’ and *‘rejection’* are final decisions issued by HSA.

For an *‘approvable’* application, the applicant will be informed of the conditions for approval in writing and is required to fulfil these conditions within a stipulated timeframe prior to the grant of a final approval.

For a *‘non-approvable’* application, the applicant will be informed of the deficiencies leading to the non-approvable decision in writing. If the applicant wishes to address the specified deficiencies, the response should be based on the original data set submitted to HSA and furnished within the stipulated timeframe. New data not previously reviewed by HSA during the evaluation of the application concerned will not be accepted.

An application will be considered withdrawn if the applicant fails to reply within the stipulated timeframe subsequent to an *‘approvable’* or a *‘non-approvable’* decision. Once the application is withdrawn, it is considered closed and the applicant will be required to make a new application if he wishes to pursue the regulatory approval for the product concerned.

Upon an *‘approval’* regulatory decision, the product will be added to the [Register of Therapeutic Products](#).

HSA may register the product subject to post-approval commitments. In such circumstances, the applicant will be required to furnish a letter of commitment stating the undertakings concerned.

Applicants must take note of the registration conditions and the post-approval commitments specified in the registration. The registration conditions can be viewed at Enquiry@PRISM.

10 POST-APPROVAL CHANGES

Upon the registration of a product, product registrants are responsible for ensuring the product's quality, efficacy and safety through its life cycle.

HSA must be notified of any changes to the product's quality, efficacy and safety as per [Chapter F](#) of this guidance.

11 TARGET PROCESSING TIMELINES

Please refer to Appendix 5 for information on target processing timelines for the different application types and evaluation routes.

12 FEES

As the fees may be subject to revision from time to time, applicants are advised to visit the [HSA website](#) for updated information on fees .

Payment can be made via GIRO or other electronic payment modes such as eNets or eCredit card.

NOTE: Applicants are strongly encouraged to apply for a GIRO account ([click here for GIRO application form](#)) with HSA to facilitate payments for future submissions and subsequent payment for retention fee for the registered products.

12.1 Screening Fee

A screening fee is payable at the time of online submission via PRISM and is non-refundable once the application is submitted via PRISM.

For payment via GIRO, the screening fee will be debited upon the successful submission of an online application.

For payment via other electronic payment modes, the screening fee must be paid before the application is considered successfully submitted online.

12.2 Evaluation Fee

An evaluation fee is payable upon the acceptance of the dossier for evaluation and is non-refundable once the application is accepted.

For payments via GIRO, the evaluation fee will be debited upon the acceptance of the application.

For payments via other electronic payment modes, the evaluation fee will be collected together with the screening fee. In the event that the application is not accepted for evaluation, the fee collected will be refunded to the applicant .

Applicants may opt for the progressive payment scheme. This is an **opt-in** scheme eligible for applicants who make payment via GIRO and is only applicable to the application types listed in Table 3:

Table 3 Product Applications Applicable for Progressive Payment Scheme

Percentage of Evaluation Fee Payable at Each Stage					
Application Type	Evaluation Route	Evaluation Status			
		Acceptance for Evaluation	Active Evaluation in Progress	Evaluation at Midway	Completed Evaluation
NDA-1 NDA-2 NDA-3	Full or Abridged	30%	40%	20%	10%
GDA-1 GDA-2	Abridged, Verification or Verification -CECA				

Once the application is submitted, the selected payment scheme (full or progressive) cannot be amended. Applicants who wish to change their selected payment scheme will have to withdraw and re-submit the application(s); and any upfront payment made (e.g. screening fee) are non-refundable.

For applications under the progressive payment scheme, in the event that the application is withdrawn during the evaluation stage, any fees that had been charged, but not debited from the GIRO account would remain payable. Any paid fee is non-refundable.

12.2.1 Changes to Application Types and Re-routing of Evaluation During Screening

If an application type or evaluation route is incorrectly selected, applicants will be informed via an Input Request. Such changes may result in a different **evaluation fee** upon acceptance of the application.

In the situation where the applicant decides not to pursue the application due to the said changes, the screening fee is not refundable.

For applications which require withdrawal and resubmission, the screening fee is not refundable. Applicants may wish to seek clarification on the appropriate application type or evaluation route via the [online feedback form](#) on the HSA website prior to the submission.

12.2.1.1 Change of Sub-Type within the Same Application Type

This refers to a change in the sub-type of the selected application type (e.g. from NDA-1 to NDA-2, NDA-2 to NDA-3, or GDA-1 to GDA-2).

The applicant will be informed of the change via an Input Request. However, applicants should **not** amend the application type field in the PRISM application form. The change will be effected by HSA at the point of acceptance of the application.

In the situation where the applicant decides not to pursue the application due to the said change, the applicant must withdraw the application prior to acceptance to avoid the evaluation fee being charged.

12.2.1.2 Change of Application between Different Application Types

This refers to a change in the application type between GDA to NDA or *vice versa*.

The applicant will be required to withdraw and resubmit the application if the applicant intends to pursue the application.

12.2.1.3 Change of Evaluation Route

This refers to a change in evaluation route (e.g. Full to Abridged, Verification to Abridged, Abridged to Verification, etc.).

The applicant will be required to withdraw and resubmit the application if the applicant intends to pursue the application.

CHAPTER C NEW DRUG APPLICATION SUBMISSION

This chapter applies to new drug applications for products containing new chemical and biological entities. Applicants are advised to refer to [Chapter E](#) for new drug applications for biosimilar products.

13 APPLICATION TYPES

NDA New Drug Application

NDA-1: For the first strength of a product containing a new⁶ chemical or biological entity.

NDA-2: (a) For the first strength of a product

- (i) containing a new combination of registered chemical or biological entities;
- (ii) containing registered chemical or biological entity(ies) in a new dosage form (e.g. tablets, capsules, injectables), new presentation (e.g. single-dose vials, multi-dose vials, pre-filled syringe) or new formulation (e.g. preservative-free);
- (iii) containing registered chemical or biological entity(ies) for use by a new route of administration; or
- (iv) containing registered chemical or biological entity(ies) for new indication(s), dosage recommendation(s) and/or patient population(s).

(b) For products that do not fall under the requirements for NDA-1, NDA-3 or GDA.

NDA-3: For subsequent strength(s) of a product that has been registered or has been submitted as an NDA-1 or NDA-2. The product name, dosage form, indication, dosing regimen and patient population should be the same as that for the NDA-1 or NDA-2.

⁶ i.e. not a currently registered entity in Singapore.

14 EVALUATION ROUTES

There are three evaluation routes for an NDA – full, abridged and verification evaluation routes. The eligibility criteria are different for each evaluation route. Applicants should be familiar with the criteria for each evaluation route because each route has different documentary requirements.

Figure 3 is a schematic diagram illustrating the evaluation routes for NDAs:

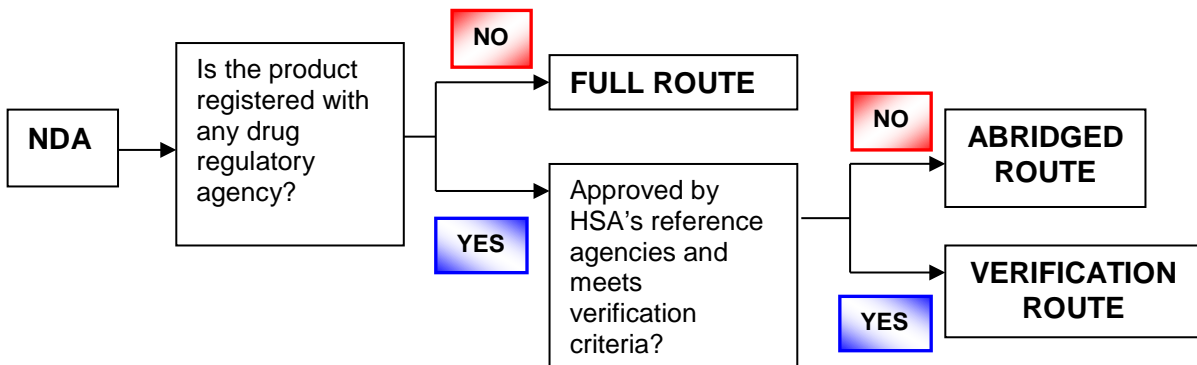


Figure 3 Schematic Diagram of Evaluation Routes for NDAs

14.1 Full Evaluation Route

Full evaluation applies to a product that has not been approved by any drug regulatory agency at the time of submission.

For a submission under the full evaluation route, the applicant is required to notify HSA via the [online feedback form](#) on the HSA website at least two months prior to the intended submission date of the application dossier. The notification should include information on the product name (if available), active ingredient(s), summaries of the quality, non-clinical and clinical data (e.g. Module 2.4 Non-clinical Overview, Module 2.5 Clinical Overview), planned submissions in other countries, and the planned date of submission to HSA.

14.2 Abridged Evaluation Route

Abridged evaluation applies to a product that has been approved by at least one drug regulatory agency at the time of submission.

14.2.1 Priority Review

For NDAs submitted via the abridged evaluation route, the applicant may request for priority review for a life-saving drug if there are unmet medical needs. The following are the criteria that will be considered for granting a priority review:

- (a) The drug is intended for the treatment of a serious life-threatening condition and demonstrates the potential to address local unmet medical needs, as defined by:
- (i) the absence of a treatment option; or
 - (ii) the lack of safe and effective alternative treatments, such that the drug would be a significant improvement compared to available marketed products, as demonstrated by
 - (A) evidence of increased effectiveness in treatment, prevention, or diagnosis;
 - or
 - (B) elimination or a substantial reduction of a treatment-limiting drug reaction.
- (b) Disease conditions that are of local public health concern will be given primary consideration for priority review. Currently these include:
- (i) cancer; and
 - (ii) infectious diseases: dengue, tuberculosis, hepatitis and malaria.

The request for priority review should be made at the point of the application submission and accompanied by justifications (attached in PRISM; see [section 15.1 – Introduction \(CTD/PRISM section 1.3\)](#)) for requesting for a priority review and how the product is expected to benefit patients, as substantiated by the following evidence:

- The seriousness of the disease condition, local and worldwide mortality rates, anticipated morbidity and debilitation as a consequence of the disease;
- Local epidemiology data and volume of requests through the exemption route on a named-patient basis;
- The unmet needs, current available treatment options and standard therapies, and the inadequacy of current therapies;

- The extent to which the product is expected to have a major impact on medical practice, its major benefit, and how it addresses the unmet needs; and
- Clinical evidence supporting the claims of significant improvement compared to available treatments.

HSA reserves the right to deny a request for priority review if it is deemed appropriate. The decision for the granting of priority review would be conveyed to the applicant at the point of acceptance of the application for evaluation.

14.3 Verification Evaluation Route

Therapeutic products with similar indication(s), dosing regimen(s), patient group(s), and/or direction(s) for use that have been approved by at least two of HSA's reference drug regulatory agencies may be submitted via the verification evaluation route. HSA's reference drug regulatory agencies are:

- Australia Therapeutic Goods Administration (TGA);
- Health Canada (HC);
- US Food and Drug Administration (FDA);
- European Medicines Agency (EMA) via the Centralised Procedure; and
- UK Medicines and Healthcare Products Regulatory Agency (UK MHRA) via
 - the national procedure, or
 - as the Reference Member State (RMS) via the Mutual Recognition Procedure or Decentralised Procedure.

However, approval by these reference drug regulatory agencies does not oblige HSA to approve the application. HSA may also re-categorise applications to other evaluation routes if deemed appropriate.

One of the reference drug regulatory agencies must be declared as the primary reference agency. The chosen primary reference agency is defined as the reference drug regulatory agency from which the qualifying supporting documents (as outlined in this guidance) will be submitted.

Additional eligibility criteria for the verification route include:

-
- The application must be submitted to HSA within three years from the date of approval by the chosen primary reference agency;
 - A declaration letter issued by the product owner/applicant must be provided stating that all aspects of the drug product's quality, including but not limited to the formulation, manufacturing site(s), release and shelf life specifications and primary packaging, are identical to that currently approved by the chosen primary reference agency at the time of submission. However, a different container closure system type (e.g. Alu/Alu blister vs. HDPE bottle) may be proposed to meet ASEAN stability requirements;
 - If a Drug Master File is submitted, then a separate declaration letter issued by the applicant must also be provided to state that the DMF submitted to HSA is identical to that submitted to the chosen primary reference agency;
 - The product does not need a more stringent assessment as a result of differences in local disease patterns and/or medical practices (e.g. some anti-infectives);
 - The product and its intended use – i.e. indication(s), dosing regimen(s) and patient group(s) – have not been rejected, withdrawn, or approved via appeal process or are not pending deferral by a drug regulatory agency for safety and/or efficacy reasons; and
 - The product is not a biological product.

The proposed indication(s), dosing regimen(s), patient group(s) and/or direction(s) for use should be the most stringent among those approved by the reference drug regulatory agencies. In the event that the chosen primary reference agency does not bear the most stringent indication(s), dosing regimen(s), patient group(s) and/or direction(s) of use, the clinical assessment report from the reference drug regulatory agency that does meet these requirements should be submitted. Reports from the public domain are acceptable. The proposed PI/PIL should be identical to that approved by this reference drug regulatory agency (with the exception of country-specific information).

For a product with a proposed indication that has been designated as an Orphan Drug by at least one reference drug regulatory agency or a product that has been approved by at least one reference drug regulatory agency via an accelerated/fast-

track approval, approval under exceptional circumstances or equivalent approval process, the applicant should consult HSA on the eligibility of such a product through the verification route prior to its submission.

14.3.1 NDA-3 Applications

For the NDA-3 application type, the verification evaluation route may be applied to the registration of subsequent strengths of a **currently-registered** product in Singapore. To qualify for the verification evaluation route for an NDA-3 application:

- if the product has been evaluated and approved by at least **one** of HSA's reference drug regulatory agencies, then the NDA-3 must be submitted within two years from the date of approval by that reference drug regulatory agency; or
- if the product has been evaluated and approved by at least **two** of HSA's reference drug regulatory agencies, then the NDA-3 must be submitted within three years from the date of approval by the chosen primary reference agency.

All other eligibility criteria for the verification evaluation route as stated in [section 14.3](#) above will apply to NDA-3 applications except for the following:

- The proposed indication(s), dosing regimen(s), patient group(s), and/or direction(s) for use must be **identical** to the corresponding approved NDA-1 and/or NDA-2 product(s); and
- The proposed PI/PIL should also be consistent with that currently approved for the corresponding NDA-1 and/or NDA-2 product(s).

15 DOCUMENTARY REQUIREMENTS

Table 4 outlines the CTD Modules/Parts required for NDAs submitted under each evaluation route:

Table 4 Dossier Submission Requirements for NDAs

Documents	Location in		Module/Part required for		
	ICH CTD	ACTD	Full NDA	Abridged NDA	Verification NDA

Administrative Documents	Module 1	Part I	Yes	Yes	Yes
Common Technical Document Overview and Summaries	Module 2	<i>Incorporated in Parts II, III and IV</i>	Yes	Yes	Yes
Quality documents	Module 3	Part II	Yes	Yes	Yes
Non-clinical documents	Module 4	Part III	Yes	ICH: No [#] ACTD: Overview only	ICH: No [#] ACTD: Overview only
Clinical documents	Module 5	Part IV	Yes	Study report(s) of pivotal studies and synopses of all studies (phase I-IV) relevant to requested indication, dosing and/or patient group	Study report(s) of pivotal studies and synopses of all studies (phase I-IV) relevant to requested indication, dosing and/or patient group

[#]Non-clinical overview included in Module 2 of the ICH CTD.

15.1 Administrative Documents

The administrative documents relate to Module 1 of the ICH CTD or Part I of the ACTD and are applicable to all evaluation routes for NDAs. The following sections are to be submitted:

Cover Letter (to attach under CTD/PRISM section 1.2 - Introduction)

To include a cover letter stating the PRISM application number of the submission, the product name, and the number of CD/DVDs submitted in the application dossier.

Comprehensive Table of Contents (CTD/PRISM section 1.1)

The comprehensive table of contents is a complete list of **all** documents provided in the application dossier listed by Module/Part. The location of each document should be identified by the Module/Part number.

NOTE: Applicants must complete the relevant checklist found in Appendix 2A or Appendix 3A and attach the completed checklist under PRISM section 1.2

Introduction (CTD/PRISM section 1.2)

Applicants should give a concise summary of the application and justify the need for the application – for example, whether the product presents an advantage to patient groups in terms of improved quality, safety and efficacy compared to available alternatives.

Applicants should also justify the lack of certain documents within the dossier and deviation from the guidelines, if any.

Requests for priority review should be stated in the Introduction, and the justification document appended in this section.

Labelling, Package Insert and Patient Information Leaflet (CTD/PRISM section 1.4)

All proposed labels are to be submitted for registration in Singapore. Applicants are required to provide the artwork/drafts of the proposed Singapore product labels, PI and/or PIL for the product. The submission of the proposed PI or PIL is dependent on the forensic classification of the product to be registered, as described in Table 5:

Table 5 Submission of Proposed PI or PIL According to Forensic Classification in Singapore

	Forensic Classification in Singapore		
	POM	P	GSL
Package Insert (PI), also known as prescribing information, SPC, or product monograph	Required	<i>Optional</i>	<i>Optional</i>
Patient Information Leaflet (PIL), also known as consumer medicine information (CMI)	<i>Optional, unless warranted</i>	Required	Required

One PI and/or PIL should be registered for each product application. If multiple manufacturing sites are proposed for registration, information for all sites should be included in one PI and/or PIL. If there are different strengths or dosage forms, the submission of one common PI/PIL for all strengths or dosage forms is encouraged. If separate PI/PILs are to be registered for different strengths or dosage forms, the content should be consistent across the PI/PILs, except for strength/dosage form-specific information.

All artwork and drafts should be legible. The draft artwork of the outer carton and inner/blister labels should be consistent with the format, design and colour that are to be printed. Separate labels must be submitted for each different pack size of the drug product.

Handwritten information is not acceptable, with the exception of statements such as 'batch number and expiry dates will be printed' or similar on the outer carton or inner/blister labels. Movable text boxes/pictures placed over other hidden information/text are also not acceptable.

The product labels, PI and/or PIL must be in English. If non-English text is included in the labelling, applicants must provide an official statement to declare that the non-English text is complete, accurate and unbiased information and is consistent with the English text.

Appendix 7 contains specific details on the product labelling requirements for Singapore.

Approved SPC/PI/PIL (CTD/PRISM section 1.5)

In this section, the applicant should submit the following:

- (a) the approved SPC, PI and/or PIL from the drug regulatory agency that issued the proof of approval; and
- (b) the approved SPC, PI and/or PIL from **all** of HSA's reference drug regulatory agencies, where applicable.

The country from which the submitted SPC, PI and/or PIL originates should be appropriately indicated (e.g. in the document file name).

Assessment Report from Reference Agencies (CTD/PRISM section 1.6)

This section refers only to applications submitted under the verification evaluation route. Assessment reports and supporting documents issued by the primary reference agency and inserted into this section must be unredacted and unedited. Applicants should refer to [section 15.6.3](#) for specific details on the required documents.

Description of Batch Numbering System (CTD/PRISM section 1.7)

Detailed information on the system of assigning unique codes to different production batches of the product should be provided to allow for batch identification. Where applicable, examples of the batch numbering system should be included to illustrate how the batch number enables identification.

Proof of Approval (CTD/PRISM sections 1.8, 1.9)

Proof of approval is not required for NDAs undergoing a full evaluation.

For an abridged evaluation of an NDA, proof of approval from any drug regulatory agency is required. Proof of approval must come in the form of:

- an official approval letter, or equivalent document (e.g. Certificate of Pharmaceutical Product; CPP), which certifies the registration status of the drug product; and

-
- the SPC, PI and/or PIL approved by the drug regulatory agency that issued the approval letter.

For a verification evaluation of an NDA, proof of approval from at least two (or at least one or two for NDA-3, depending on the eligibility criteria stated in [section 14.3.1 NDA-3 Applications](#)) of HSA's reference drug regulatory agencies, including the chosen primary reference agency, is required. Proof of approval must come in the form of:

- an official approval letter, or equivalent document (e.g. Certificate of Pharmaceutical Product; CPP), which certifies the registration status of the drug product; and
- the SPC, PI and/or PIL approved by the drug regulatory agency that issued the approval letter.

If the SPC is in a non-English language, applicants should refer to [section 6.2.2 Language and Translation](#) for more information on acceptable translations.

Note that all aspects of the product's quality and intended direction(s) for use in Singapore should be the same as those approved by the drug regulatory agency that issued the approval letter.

Certificate of Pharmaceutical Product (CPP) should be valid at the time of submission and should comply with WHO format (refer to [Model certificate of a pharmaceutical product](#)). It is not required for information such as the product formula, manufacturing sites, etc. to be reflected on the CPP, but if such information are present in the CPP, the information should be consistent with that proposed for the Singapore market. Note that CPPs that indicate that the product is not licensed in the exporting country (including scenario where the product is licensed for "solely for export only") are not acceptable proof of approval.

Approval letters should either be an original copy or a certified true copy and in English. Applicants should refer to [sections 6.2.2 Language and Translation](#) and [6.2.3 Certifying Non-Original Documents](#) for more details. Reference to drug regulatory authority websites in the form of website screenshot and URL (for the

website) for confirmation of the approval status of the products by that regulatory authority are acceptable, provided that the product's identity and product's ownership can be confirmed from that website.

HSA reserves the right to request for a Certificate of Pharmaceutical Product (CPP), if deemed appropriate.

If the brand name (trade name) of the product registered in the country which issued the proof of approval is different from that proposed in Singapore, the applicant is required to submit a declaration letter from the product owner to declare that both products marketed under the different brand names are **identical** in all aspects of quality, safety and efficacy except for the brand name.

Authorisation Letters (CTD/PRISM section 1.10)

All submitted authorisation letters should be on the authorising company's (i.e. product owner's) letterhead, dated and signed by the designated authorised person in the company.

If the product owner is not the local applicant, manufacturer and/or batch releaser; or the product owner's address is different from that of the local applicant, manufacturer and/or batch releaser, then the following authorisation letter(s) must be submitted:

- (a) *from Product Owner to the Applicant (Company) (1.10.1)* – this letter authorises the local applicant to apply for and be the product registrant for a specific therapeutic product (product name to be stated as in PRISM) and be responsible for all matters pertaining to the registration of this product in Singapore.
- (b) *from Product Owner to Manufacturer (1.10.2)* – this letter authorises the specified manufacturer to produce, pack and/or label the drug product intended for Singapore. If there are multiple drug product manufacturers, then the applicant may opt to submit one authorisation letter which clearly states all of the manufacturers (names and addresses) and their responsibilities relating to the drug product (such as the manufacturing operation of each manufacturer in relation to the product being submitted). For biologic drug products, an additional

authorisation letter from the product owner to the drug substance manufacturer is required.

- (c) *from Product Owner to Batch Releaser (1.10.3)* – this letter authorises the specified company to batch release the drug product. If there are multiple sites responsible for the batch release of the product, then the applicant may opt to submit one authorisation letter which clearly states all of the batch releasers (names and addresses) and their responsibilities.

The applicant may also issue an authorisation letter to authorise the specified secondary packager located in Singapore to pack and/or label the drug product intended for Singapore.

Applicants are to ensure that all names and addresses in the authorisation letters are consistent with the information provided in PRISM and the dossier. For manufacturers and batch releasers, the actual site address of the named company should be stated in the letter(s) – i.e. do not state the office address. Any discrepancy found will delay the registration process.

All authorisation letters should also state specific product details, including the product name, dosage form and strength as stated in the PRISM application form.

Applicants also have the option to combine the authorisation letters as stated above into one document, provided that all names, addresses and responsibilities are clearly stated.

GMP Certification/Proof of GMP Compliance (CTD/PRISM section 1.11)

Documentary evidence must be provided to certify that the manufacturer(s) complies with current applicable GMP standards. Applicants must submit a GMP certificate issued by a drug regulatory agency for all drug product manufacturing sites including, but not limited to, bulk product manufacturers, primary packagers and secondary packagers.

A CPP may be submitted *in lieu* of a GMP certificate provided that the manufacturer's name(s) and address(es) is(are) stated on the CPP and the CPP

states that the certifying authority conducts periodic inspection of the manufacturing plant in which the dosage form is produced. Applicants should note that the names and addresses of all manufacturers should be consistent throughout the application – i.e. GMP certificate, Letter of Authorisation, CTD sections S2.1 and P3.1 and PRISM.

[EudraGMP](#), the database of the European Community of manufacturing authorisations and of certificates of good manufacturing practice, is an acceptable alternative proof of GMP compliance *in lieu* of a GMP certification. Applicants making reference to the EudraGMP as the proof of GMP compliance should provide a screen capture of the EudraGMP website for the specific finished product manufacturing site, as well as the URL to the website.

Certain accreditation documents/certificates issued by other drug regulatory agencies (for example, Japan/PMDA Accreditation Certificate of Foreign Drug Manufacturer, US/FDA Establishment Licence, Canada/Health Canada Establishment Licence) are not acceptable proof of GMP compliance.

Proof of GMP compliance must be valid at the time of submission to HSA and must be in English. Applicants should refer to [section 6.2.2 Language and Translation](#).

If the submitted proof of GMP compliance is no longer valid or has less than 1 month's validity at the time of acceptance of the application for evaluation, HSA reserves the right to request for a commitment letter from the applicant to submit an updated and valid proof of GMP compliance by a specified date post-acceptance.

It should be noted that diluents used for reconstituting the drug product and are packaged together with the drug product will be considered as part of the final drug product. Thus, manufacturer(s) of the supplied diluent(s) must follow the same requirements applicable to the drug product, e.g. provide proof of GMP compliance.

For biologic NDA applications, proof of GMP compliance for the drug substance must be submitted in addition to the aforementioned GMP requirements.

For products manufactured in the USA or Canada, if the applicant is unable to obtain any proof of GMP compliance (in the form of a CPP or GMP certificate) from either US FDA/Health Canada or other drug regulatory agencies, the applicant is required to submit the latest Establishment Inspection Report (EIR) issued by US FDA or Inspection Exit Notice issued by Health Canada, and any other relevant supporting documents⁷ as proof of GMP compliance. The applicant is also required to provide the following information if not found in the inspection reports:

- the last date of audit by US FDA/Health Canada;
- the approved dosage forms;
- any licensing conditions or restrictions;
- the scope of the inspection; and/or
- objective evidence and the date of a satisfactory close-out of the latest inspection conducted by US FDA/Health Canada.

For products manufactured in Switzerland, if the applicant is unable to obtain any proof of GMP compliance (in the form of a CPP or GMP certificate) from either SwissMedic or other drug regulatory agencies, the Manufacturer's Licence issued by SwissMedic is an acceptable documentary GMP evidence.

If the drug product is manufactured by a new overseas **drug product manufacturing site** not previously registered with HSA before 1st April 2004, a GMP Conformity Assessment will be conducted by HSA. Thus, when applicable, applicants must also submit the [application form to request for GMP Evidence Evaluation or for an Overseas GMP Audit](#) with the required documents to the Therapeutic Products Branch (as part of the product registration application) as stipulated in the [Guidance Notes on GMP Conformity Assessment of an Overseas Manufacturer](#).

In general, a GMP Conformity Assessment is applicable to each specific manufacturer, dosage form, manufacturing activities and applicant company. This also includes contract manufacturers who perform certain manufacturing activities,

⁷ Any other supporting document which declares GMP compliance of the manufacturing site in the US and signed by an official of the US FDA.

such as terminal sterilisation of the drug product, mixing of excipient with drug substance (drug product intermediate), etc.

In general, applicant companies with active product registration that included the finished product manufacturer(s) performing the same manufacturing activities (excluding parametric release) for the same dosage form would not be required to undergo another GMP Conformity Assessment by HSA when they submit a new product application which included the same finished product manufacturer(s).

For drug product manufacturing sites that use parametric release (e.g. where a terminally sterilised product is released based on the review of manufacturing process data instead of sterility testing), a GMP Conformity Assessment is required for overseas drug product manufacturers. Eligibility criteria for such applications for overseas manufacturing sites are:

- a) Country of origin must be a PIC/S country; and
- b) Parametric release is approved by the local authority.

If the above criteria are met, then approval letter and recent documentary evidence of approval status (e.g. GMP Certificate) for parametric release issued by the local authority should be provided. The manufacturing site and the product proposed for parametric release should be clearly stated on these documents.

For a local manufacturing site that would like to apply for parametric release, applicants are advised to contact HSA prior to submission as pre-approval inspection is required.

HSA reserves the right to request for a GMP Conformity Assessment if deemed necessary, or to request for additional or updated documents as evidence of GMP compliance during the course of the registration process. HSA also reserves the right to conduct an audit of any overseas manufacturer irrespective of the documentary GMP evidence that is approved by HSA or any other PIC/S member authorities, if deemed appropriate.

If in doubt whether a GMP Conformity Assessment by HSA is required for the manufacturing sites included in the submission, applicants are encouraged to complete and submit applications to request for GMP Conformity Assessment with the product registration application, and HSA will advise accordingly whether the GMP Conformity Assessment would be required.

Patent Declaration (CTD/PRISM section 1.12)

A signed and dated patent declaration form is required for each NDA. Applicants should refer to [section 3](#) for information on patent linkage and Appendix 1 for the Patent Declaration Form template.

Guiding notes on filling the Patent Declaration form are provided below.

- (a) Section 1 '*Applicant Particulars*' - state the name and address of the local company.
- (b) Section 2 '*Product Particulars*' - state the product name, name and strength of active ingredient and dosage form. All product particulars should be consistent with that stated in the product labels and other relevant documents as submitted in PRISM.
- (c) Section 3 '*Application Category*' - declare the patent category that the application falls under (with respect to a Singapore Patent as registered with IPOS).
- (d) Section 4 '*Information for Category A1 Applications*' - applicable if category A1 is selected in Section 3.
- (e) Section 5 '*Information for Category A2 Applications*' - applicable if category A2 is selected in Section 3. Check the box which is relevant and provide details of the patent in force.
- (f) Section 6 '*Information for Category A3 Applications*' - applicable if category A3 is selected in Section 3. Provide details of the patent in force.
- (g) Section 7 '*Information for Category B Applications*' - applicable if category B is selected in Section 3. Check the box which is relevant and provide details of the patent in force.
- (h) Section 8 '*Declaration*' - the patent declaration must be signed by the person authorised to make the declaration on behalf of the company named in Section 1. The authorised person is ordinarily an officer of the company such as

Company Director or Company Secretary as registered with ACRA, or equivalent. Evidence of such authorisation is to be submitted together with the declaration.

Evidence of authorisation for Section 8 of the form can be in the form of:

- An ACRA printout⁸ ([BizFile](#)) listing the Company Directors/Secretary;
- A resolution of board of directors;
- A resolution of a general meeting of the company; or
- An extract of the relevant portion of the company's articles of association.

Declaration forms must bear the signatures of the authorised person and the company stamp of the applicant.

NOTE: The applicant should ensure that the information provided in the patent declaration form and the evidence of authorisation are current at the point of application submission.

The patent declaration form needs to be submitted twice – at the time of submitting the application for registration and prior to the issuance of the regulatory decision for registration (upon request by HSA), if the dossier was deemed satisfactory with respect to the product's safety, efficacy and quality aspects.

Declaration on Rejection, Withdrawal and Deferral (CTD/PRISM section 1.13)

The document required for this section is a declaration letter issued by the product owner or applicant that states that the application submitted to HSA and the directions of use including indication(s), dosing regimen(s) and patient population(s)

- have not been rejected or withdrawn;
- have not been approved via an appeal process; and
- are not pending deferral

by any drug regulatory agency. If any of the above conditions apply to the application, details and reasons must be provided to HSA.

⁸ The required information on the company's business profile should be obtained directly from ACRA's website ([BizFile](#)).

Declaration for NDA Verification (CTD/PRISM section 1.14)

This section applies only to the verification evaluation route.

A declaration letter issued by the product owner/applicant must be provided to state that all aspects of the product's quality are identical to that currently approved by the chosen primary reference agency at the time of submission. Quality aspects include, but are not limited to, formulation, manufacturing site(s), release and shelf life specifications, and primary packaging. However, a different container closure system type (e.g. Alu/Alu blister vs. HDPE bottle) may be proposed to meet ASEAN stability requirements.

If a Drug Master File is submitted, then a separate declaration letter issued by the applicant must also be provided to state that the DMF submitted to HSA is identical to that submitted to the chosen primary reference agency.

Registration Status in Other Countries (CTD/PRISM section 1.15)

The registration status of the product in other countries should be entered into PRISM section 4.9 – refer to Appendix 17 for further details.

In the event that the PRISM text space does not allow the input of the full details of the indication(s) and/or reason(s), a brief description may be entered. The full details should then be attached in softcopy (PDF) in PRISM section 7 (Supporting Attachments). The document should be in the format shown in Table 6:

Table 6 Example of a Table of Information on Registration Status in Other Countries for CTD Section 1.15

Country	Application status	Status Date	Approved application indication/dosing regimen details[#]	Approved forensic classification⁺
<i>Country 1</i>	<i>Approved</i>	<i>12 Jan 2005</i>	<i>Adjuvant treatment of colorectal cancer stage III (Dukes C) following complete resection of primary tumour.</i>	<i>POM</i>
<i>Country 2</i>	<i>Approved</i>	<i>2 Feb 2006</i>	<i>Adjuvant treatment of colorectal cancer following surgery</i>	<i>POM</i>
<i>Country 3</i>	<i>Withdrawn by applicant</i>	<i>14 Apr 2002</i>	<i>Indication submitted 'Adjuvant treatment of colorectal cancer'. Withdrawn due to insufficient long term efficacy data (only phase II data submitted). Re-submitted on 16 June 2005 with completed phase III data for 'Adjuvant treatment of colorectal cancer following surgery'.</i>	<i>POM</i>

Country	Application status	Status Date	Approved application indication/dosing regimen details [#]	Approved forensic classification ⁺
Country 4	Approved	21 Nov 2004	Adjuvant treatment of colorectal cancer stage III (Dukes C) following complete removal of primary tumour. Notice of Compliance with Conditions issued on 16 April 2003 based on promising efficacy results with condition to furnish confirmatory efficacy data.	POM
Country 5	Pending	Submitted: 15 Jun 2005	Adjuvant treatment of colorectal cancer stage III (Dukes C) following surgery.	POM

[#] Applicable to information on reference agencies, Country of Origin, and all rejections/withdrawals/deferrals

⁺ Applicable to information on reference agencies and Country of Origin.

Confirmation of Reference Agency's Approval of Chemistry & Manufacturing Control (CMC) Aspects (CTD/ PRISM section 1.16)

For applications submitted under the abridged evaluation route for a chemical drug and for which approval was obtained from at least one of HSA's reference agencies not more than 5 years before the date of submission to HSA, a colour scanned copy of the completed Dossier Clarification Supplement should be submitted in PRISM (refer to Appendix 18 *Confirmation of Quality Dossiers with Reference Agency's Approval* for more information).

15.2 CTD Overview and Summaries

The ICH or ASEAN CTD overview and summary documents are to be inserted into Module 2 of the ICH CTD or into the relevant sections in Part II, III and IV of the ACTD. The ICH or ASEAN Quality Overall Summary can be submitted either in Word or PDF format.

Overview and Summaries	Location in CTD	
	ICH CTD	ACTD
Quality Overall Summary	Module 2, section 2.3	Part II, section B
Non-clinical Overview & Summaries	Module 2, section 2.4 & 2.6	Part III, sections B & C, respectively
Clinical Overview & Summaries	Module 2, section 2.5 & 2.7	Part IV, sections B & C, respectively

15.3 Quality Documents

The quality documents relate to Module 3 of the ICH CTD or Part II of the ACTD. In addition to the ICH or ACTD technical content requirements, the following explanatory notes pertain to requirements specific to Singapore:

15.3.1 Body of Data – Drug Substance

The [ICH M4Q technical guideline](#) and [ASEAN Common Technical Requirements \(ACTR\)](#) provide details on the information to be included in the drug substance sections of an application dossier.

NOTE: If a drug product contains more than one drug substance, the information within Module 3.2.S (ICH CTD) or Part II.S (ACTD) must be provided in its entirety for each drug substance.

All of the drug substance sections of the CTD – i.e. S.1 to S.7 – should be submitted in the application. If these sections are incomplete, then the dossier should make

reference to a Drug Master File (DMF), Plasma Master File (PMF) or Certificate of Suitability of Monographs of the European Pharmacopoeia (CEP).

Because the drug product manufacturer is responsible for the quality control of the drug substance that is used in the drug product, applicants should note that the complete S section of the CTD dossier should be provided by the drug product manufacturer regardless of whether a DMF or a CEP has been submitted in support of a product application.

Drug Master File (DMF)

A Drug Master File (DMF) is a compilation of information on facilities, processes or components used in the manufacturing, processing, packaging and storing of a drug that is submitted to the HSA. A DMF contains confidential information and is submitted solely at the discretion of the DMF holder.

A DMF is submitted in support of a therapeutic product application, and will be reviewed only in connection with the review of an application. As such, a separate approval will not be issued for a DMF.

Appendix 11 describes the DMF process and documentary requirements for DMF submission.

Plasma Master File (PMF)

A Plasma Master File (PMF) is required whenever a human plasma-derived product is used either as a drug substance or as an excipient, as the PMF contains information on the collection and control of source materials. The PMF may be submitted either as a stand-alone document or as part of the application dossier. Appendix 8 describes the PMF data requirements for submission.

If the PMF is a stand-alone document, then it should be filed separately from the application dossier for pre-marketing evaluation. The applicant may cross-reference a PMF that is currently registered with HSA where applicable.

Certificates of Suitability (CEP)

A Certificate of Suitability is a document issued by the European Directorate for the Quality of Medicines and Healthcare (EDQM) that certifies the quality of a drug substance in compliance to the Ph. Eur. A CEP may be submitted *in lieu* of the CTD S Section or a DMF.

If reference is made to a CEP, the applicant should submit a copy of the duly authorised, valid CEP, including all annexes. A duly authorised CEP should contain the following information in the '*Declaration of Access*' section of the CEP:

- name of the Product Owner or local applicant;
- name of the product to be registered – it is recommended that the dosage form and strength(s) also be stated;
- signature and company stamp of the CEP holder; and
- date of authorisation.

The following additional requirements apply for CEP-based submissions:

- (a) If Ph. Eur. standard is claimed for the drug substance, the relevant CTDs should be submitted:
- (i) S.2.1;
 - (ii) S.4.1 and S.4.4 from both the drug substance and drug product manufacturers; and
 - (iii) S.6 and S.7 should be provided if the re-test period/shelf life is not stated on the CEP.
- (b) If other standards are claimed for the drug substance, the relevant CTDs should be submitted:
- (i) S.2.1;
 - (ii) S.4.1 to S.4.5 from both drug substance and drug product manufacturers; and
 - (iii) S.6 and S.7 should be provided if re-test period/shelf life is not stated on the CEP.

NOTE: HSA reserves the right to request for any additional information about the CEP-certified drug substance if it is deemed appropriate.

If there is a CEP for animal-derived material used in the drug product, the applicant may submit the CEP together with the documents stipulated in Annex 1- section 1.1 of Appendix 9 *Guideline on the Registration of Human Medicinal Products Containing Materials of Animal Origin*.

It is the applicant's responsibility to submit the latest CEP updates, with annexes, as soon as they are available from EDQM.

Control of Drug Substance (CTD section 3.2.S.4)

Batch analysis data should be provided by the drug substance and drug product manufacturers, and, if available, from the same drug substance batches. Analytical results should be provided from a minimum of two batches from each proposed drug substance manufacturer and should be sufficient to support the specification(s) as well as to demonstrate consistency in manufacturing. The batches submitted should preferably be of production scale or at least pilot scale.

Stability Data of Drug Substance (CTD section 3.2.S.7)

At the time of submission, the minimum stability data required are as follows:

- At least 12 months of long term data and 6 months of accelerated data from at least three primary batches of the drug substance; and
- The batches should be at least pilot scale-sized and manufactured by a method that simulates the final commercial process.

If the drug substance is sourced from multiple sites, stability data from each site should be provided.

HSA may request for additional stability data if deemed necessary for the evaluation of the application.

15.3.2 Body of Data – Drug Product

The [ICH M4Q](#) technical guideline and [ACTR](#) also provide details on the information to be included in the drug product sections of an application dossier. For drug product intermediates and diluents, separate drug product sections should be submitted.

Pharmaceutical Development (CTD section 3.2.P.2)

Detailed descriptions and discussions, with relevant data, which relate to the development, and hence quality, of the drug product should be provided in the relevant dossier sections. Examples include, but are not limited to:

- polymorphism, solubility or particle size of the drug substance and its effect on the product's quality;
- a description and the results of the formulation development;
- the rationale for the choice of dissolution method and a discussion of its discriminatory nature, with data;
- compatibility of the container closure system with the product or preservative efficacy test results; and
- optimisation of the manufacturing process, with data.

Process Validation (CTD section 3.2.P.3.5)

The description, documentation *and* complete results of the validation studies on the manufacturing process should be provided in the dossier in this section. Particular care should be taken to ensure that the documents include critical processes for the manufacturing process: for example, blend uniformity validation for oral dosage forms and terminal sterilisation or aseptic filling for sterile products.

Applicants should refer to the [ASEAN Guidelines on Submission of Manufacturing Process Validation Data for Drug Registration](#) and the [ASEAN Guideline on Process Validation Q&A](#) for the minimum data requirements for process validation. Other relevant international guidelines may also be referred to as appropriate.

Where ranges of batch sizes are proposed, it should be demonstrated that variations in batch size would not adversely alter the characteristics of the finished product.

For drug product manufacturing sites that use parametric release (e.g. where a terminally sterilised product is released based on the review of manufacturing process data instead of sterility testing), a more detailed discussion with supporting data on the process validation of the specific product in the proposed pack size or fill volume should be provided. In addition, risk assessment for parametric release

should be based on prior knowledge, consistency of performance of the steriliser, historical batch analysis data, risk of loading pattern/container/ contamination from the environment to product sterility, re-processing plan, etc. A detailed discussion on the control strategy should also be provided. This includes but is not limited to, a tabulation of all validated critical process parameters and loading patterns, a description of the process and requirements for the release/rejection of a batch, bioburden monitoring and control program, the segregation of sterile products from non-sterile products and the routine maintenance/re-validation program for the steriliser.

Control of Excipients (CTD section 3.2.P.4)

This section refers to all excipients used in the drug product formulation, including ingredients used in capsule shells and film coatings. The specifications and analytical method(s) for each excipient should be described, including the validation of any in-house test method(s), if applicable.

Information on proprietary ingredients, such as flavourings, colourants, coatings, perfumes and/or printing inks, should be as detailed as possible. Applicants are advised not to use internal codes but instead to give commercial names for such ingredients. In cases where the formula of the proprietary ingredient is confidential, only the total quantity of the proprietary ingredient present in the final product needs to be captured in PRISM. The formula of the proprietary ingredient should then be provided by the proprietary ingredient manufacturer directly to HSA. A declaration letter from the proprietary ingredient manufacturer should also be provided, indicating that they will inform HSA (via email to HSA_TP_Enquiry@hsa.gov.sg) should there be any change in the qualitative formulation of the proprietary ingredient.

A CoA for an excipient may be submitted *in lieu* of the excipient's specifications. If the standard claimed for an excipient is an officially recognised compendial standard, it is sufficient to state that the excipient is tested according to the requirements of that standard, rather than reproducing the specifications found in the officially recognised compendial monograph.

For excipients derived from human plasma, applicants should refer to the Appendix 8 for more information on the data requirements.

For excipients derived from animal sources, applicants should refer to Appendix 9 for more information. The checklist found in Annex 1 of Appendix 9 serves as a guide to these documentary requirements for submission. Applicants should note that the completed checklist in Annex 1 is to be submitted in CTD section 3.2.P.4.5 with the supporting documents submitted in ICH CTD section 3.2.A.2 or ACTD section Q.A.2.

For milk and certain milk derivatives such as lactose, as these excipients are generally considered non-infectious, a declaration from the supplier of the excipient stating that the milk is from healthy cows fit for human consumption and that no other potentially infectious ruminant-derived materials were used in the manufacturing process would be sufficient. This declaration is to be submitted in CTD section 3.2.P.4.5.

Control of Drug Product (CTD section 3.2.P.5)

The drug product's release and shelf-life specifications should be declared in section 3.2.P.5.1.

For the parametric release of a terminally sterilised product, the release specification and certificate of analysis should indicate that parametric release is the method used for batch release. Additionally, sterility of the product is required to be demonstrated in the stability studies even if approval for parametric release has been granted.

Descriptions of all test methods with complete validation results of all in-house methods should be submitted in sections 3.2.P.5.2 and 3.2.P.5.3.

Descriptions (including size, origin and use) and test results of all relevant batches (e.g. pre-clinical, clinical, pilot and production batches) used to establish the specification and evaluate the consistency in manufacturing should be provided.

Batch analysis data and/or CoAs from three batches of the drug product should be provided in section 3.2.P.5.4.

The justification of the specifications (section 3.2.P.5.6) should be based on scientific knowledge and data collected during product development.

Container Closure System (CTD section 3.2.P.7)

Technical information about each component of the container closure system(s) used for the drug product should be included in the dossier. The technical information to be included in the dossier includes, but is not limited to, schematic diagrams, descriptions, specifications, analytical methods, CoAs and declarations of compliance to international standards.

Stability Data of Drug Product (CTD section 3.2.P.8)

Since 01 April 2014, HSA has implemented the [ASEAN Guideline on Stability Study of Drug Product \(the 'ASEAN guideline'\)](#), a guideline on the conduct of stability studies for drug products for the ASEAN region. Applicants should familiarise themselves with this guideline prior to submission.

At the time of submission of the application, the minimum stability data required are as follows:

- At least 12 months of data under long term storage conditions and 6 months of data under accelerated storage conditions on at least three primary batches of the drug product, as per the ASEAN guideline; and
- The primary batches should be manufactured by the same method(s) and packaged in the same container closure system as that proposed for Singapore.

It is recommended that the submitted stability data be specific for the sites proposed for registration in Singapore. For example, for a proposed product, if the drug substance is sourced from two different sites (e.g. sites A and B), the minimum stability data requirements for this drug product should include one set (3 batches) for the drug product with drug substance from site A and one set (3 batches) for the drug product with drug substance from site B – i.e. a total of six batches under long term conditions and six batches under accelerated conditions.

The table below illustrates the minimum requirement at the time of submission:

E.g. For drug substance sites A and B, drug product site Z.

Dataset submitted:
3 batches of A + Z AND 3 batches of B + Z

However, if the complete set of site-specific drug product stability data is not available at the time of submission of the application for chemical drug products, then the following conditions and requirements will apply:

(a) Multiple drug substance manufacturers:

If multiple drug substance manufacturers for one drug substance of the drug product are proposed for registration, then the following dataset is the minimum requirement at the time of submission:

- (i) The full CTD S section or CEP from each drug substance manufacturer;
- (ii) The same specification used by the drug product manufacturer for control of the drug substance (the 'DP-DS specification') from all of the proposed drug substance manufacturers, should encompass the following:
 - (A) The DP-DS specification captures all test parameters and limits from all of the proposed drug substance manufacturers, unless justified;
 - (B) If the same test parameter exists among the different drug substance manufacturers (e.g. assay, degradation products), then the limit should be aligned in the DP-DS specification; and
 - (C) If different test parameters exists among the drug substance manufacturers (e.g. residual solvents), then the limit should remain the same in the DP-DS specification.

The table below illustrates common DP-DS specification:

Drug Substance site A Drug Substance specification	Drug Substance site B Drug Substance specification	Drug Product site Z Drug Substance specification
Assay 98.0-102.0%	Assay 98.0-102.0%	Assay 98.0-102.0%
Impurity A NMT 0.2%	Impurity A NMT 0.2%	Impurity A NMT 0.2%
Methanol NMT 3000ppm		Methanol NMT 3000ppm ^a
	Isopropyl alcohol NMT 5000ppm	Isopropyl alcohol NMT 5000ppm ^b
^a Applicable for Drug Substance site A only		
^b Applicable for Drug Substance site B only		

- (iii) A minimum of one set (3 batches) of drug product stability data that represents all of the proposed drug substance manufacturers; and
- (iv) If the submitted stability dataset in (iii) does not represent all of the proposed drug substance manufacturers, then a commitment letter to conduct drug product stability studies for one production-sized batch using the drug substance from each additional drug substance manufacturer that is not represented in (iii) is required.

The table below illustrates the possible submission options, which the applicant can choose one from at the time of submission:

E.g. For drug substance sites A and B (chemical drug substance only), drug product site Z.

Dataset submitted:	With commitment letter for:
Option 1: 3 batches of data using A+Z	1 production drug product batch for B+Z
Option 2: 3 batches of data using B+Z	1 production drug product batch for A+Z
Option 3: 3 batches of data using A+Z and B+Z	No commitment letter needed

Note: This approach does not apply to biological drug products – i.e. full drug substance site-specific drug product stability data are required at the time of submission.

(b) Multiple drug product manufacturers:

For biological drug products, the complete set of site-specific drug product stability data is required at the time of submission of the product application. For dossiers that are not able to meet this submission requirement, the applicant is highly recommended to discuss the issues with HSA prior to submission in order to facilitate the registration process.

If multiple drug product manufacturers for the drug product are proposed for registration, then the following dataset is the minimum requirement at the time of submission:

- (i) Drug product stability batches from each proposed drug product manufacturer should be represented;
- (ii) The number of batches from each proposed drug product manufacturer must meet the submission requirement i.e. 3 batches of drug product with:
 - A minimum of 12 months of stability data from one of the drug product manufacturer; and

- A minimum of 6 months of stability data from the other drug product manufacturer(s).

If a drug product manufacturer has manufactured development or pilot drug product batches but is not intended for registration, then the development/pilot drug product batches may be submitted in support of the proposed shelf-life and storage condition if the following dataset is submitted at the time of submission:

- The complete CTD P.3 section (process validation to be submitted, if available) from the development/pilot drug product manufacturing site;
- Batch analyses or certificates of analysis (CTD P5.4) of the stability batches from the development/pilot manufacturing site;
- Three (3) batches of a minimum of 12 months of stability data from the development/pilot manufacturing site, as per the ASEAN guideline;
- Three (3 batches) of a minimum of 6 months of stability data from the proposed drug product manufacturing site; and
- A commitment to provide the completed stability studies (up to the proposed shelf-life) from the proposed drug product manufacturing site.

The table below illustrates the possible submission options, which the applicant can choose one from at the time of submission:

E.g. For drug substance site A, drug product sites Y and Z.

Dataset submitted:
<p><u>Option 1:</u></p> <p>3 batches of a minimum 12 months stability data from one of the proposed commercial DP site (A+Y)</p> <p><u>AND</u></p> <p>3 batches of a minimum 6 months stability data from the other proposed commercial DP site (A+Z)</p>
<p><u>Option 2:</u></p> <p>3 batches of a minimum 12 months stability data from developmental/pilot DP site (A+Y)</p> <p><u>AND</u></p>

3 batches of a minimum **6 months** stability data from **proposed commercial DP site (A+Z)**

(c) Multiple drug substance and drug product manufacturers:

If multiple drug substance and drug product manufacturers are proposed for registration, then the dataset required at the time of submission will combine the requirements in (a) and (b) above.

The tables below illustrate the possible submission options, which the applicant can choose one from at the time of submission:

E.g. For drug substance sites A and B, drug product sites Y and Z

Option 1:

Site	No. of batches	
	Drug Product Site Y	Drug Product Site Z
Drug Substance Site A	2	3
Drug Substance Site B	1	0

Option 2:

Site	No. of batches	
	Drug Product Site Y	Drug Product Site Z
Drug Substance site A	3	0
Drug Substance Site B	0	3

Option 3:

Site	No. of batches	
	Drug Product Site Y	Drug Product Site Z
Drug Substance Site A	0	1

Option 4:

Site	No. of batches	
	Drug Product Site Y	Drug Product Site Z
Drug Substance Site A	3	3

Drug Substance Site B	3	2	Drug Substance Site B	0*	0*
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* *Not all drug substance sites are represented; thus, a commitment to conduct stability on one production drug product batch (from either site Y or Z) using drug substance site B is required at the time of submission.*

(d) Multiple primary packagers:

If multiple primary packaging sites for the same container closure system are proposed for registration, then the following dataset is the minimum requirement at the time of submission:

- (i) A minimum of one set (3 batches) of 12 months of stability data from one of the primary packaging sites;
- (ii) Transport validation of the bulk product to the other proposed primary packaging site(s), unless justification is provided; and
- (iii) A minimum of one set (3 batches) of 6 months of stability data from the other primary packaging site(s) with a commitment to provide the data upon completion of the stability study.

(e) Drug product stability batch(es) using development or pilot drug substance batches:

If the submitted stability dataset (3 batches) uses development or pilot drug substance batches, the stability dataset may be submitted in support of the proposed shelf-life and storage condition if the following dataset is submitted at the time of submission:

- (i) CTD S section (S2.2, S3.1, S3.2, S4.1 and S4.4) from the development/pilot drug product manufacturing site;
- (ii) One set (3 batches) of a minimum of 12 months of stability data using drug substance manufactured from developmental or pilot drug substance site;
- (iii) A commitment letter to conduct one set (3 batches) of long term and accelerated stability studies using drug substance manufactured from the

- proposed drug substance site(s), and report if any results fall outside shelf-life specifications (with proposed action) or when requested; and
- (iv) Prior to approval: To provide a minimum of 6 months of stability data as committed in (iii).

15.4 Non-clinical Documents

The non-clinical documents relate to Module 4 of the ICH CTD or Part III of the ACTD.

Applicants should refer to the [ICH CTD Guidelines M4S \(Safety\) technical guidelines](#) or the [ACTD Part III: Nonclinical guidelines](#) for detailed information on the contents of non-clinical documents for the application dossier.

15.5 Clinical Documents

The clinical documents relate to Module 5 of the ICH CTD or Part IV of the ACTD.

Guidance on how to complete this Module/Part is provided in the [ICH CTD Guideline M4E \(Efficacy\) technical guidelines](#), in particular the ICH E3 guidance document on *Structure and Contents of Clinical Study Reports*, or the [ACTD Part IV: Clinical guidelines](#).

Clinical studies should generally be conducted using the drug product formulation submitted in the application and in the appropriate patient population for the indication(s) and/or dosing regimen(s) as requested in the NDA.

Biopharmaceutic (e.g. bioavailability or bioequivalence) study reports are required if the commercial formulation for the Singapore market differs from the clinical trial formulation used in the pivotal studies.

The submission of risk management plans (RMPs) in support of all NDA-1 applications is mandatory. For NDA-2 or NDA-3 applications, HSA may also request for RMPs to be submitted on a case-by-case basis when required, following the evaluation of the safety concerns described in the product application. Guidance on

RMP submission requirements can be found in Appendix 16 *Guideline on the Submission of Risk Management Plan Documents*.

If the NDA is for a non-prescription medicine and is submitted via the abridged evaluation route, the applicant may submit a written request for a waiver of clinical data submission. Eligibility for a waiver is subject to the criteria defined in Appendix 6 *Guideline on Submission for Non-Prescription Therapeutic Products*. However, HSA reserves the right to request for the complete clinical data set if it is deemed necessary.

15.6 Specific Documentary Requirements for Each Evaluation Route

15.6.1 Full Evaluation Route

Full information on the chemical/biological development, pharmaceutical/genetic development, toxicological, pharmacological and clinical data needs to be submitted in support of the application.

The technical documents required include:

- complete quality documents for both drug substance and drug product;
- complete pharmaco-toxicological or non-clinical documents; and
- complete clinical documents, i.e. all study reports from phase I to phase III, including tables and appendices.

15.6.2 Abridged Evaluation Route

All aspects of the product's quality and direction(s) for use [including dosing regimen(s), indication(s) and patient group(s)] should be the same as that approved by the drug regulatory agency that issued the proof of approval.

The technical documents required include:

- complete quality documents for both the drug substance and drug product;
- a non-clinical overview; and
- a clinical overview, summaries of clinical efficacy and clinical safety, synopses of relevant studies, a tabular listing of the clinical development programme and

study reports of the pivotal studies (the tables and appendices to the pivotal study reports may be submitted upon request by HSA).

15.6.3 Verification Evaluation Route

The complete assessment report and other relevant supporting documents from the **chosen** primary reference agency must be submitted, as tabulated below. The assessment reports from the primary reference agency must be unredacted or unedited, and should include details of imposed licensing conditions, final product labelling, chemistry and clinical reviews, and other information in relation to the product's approval. Reports obtained from the public domain are deemed unacceptable.

Applications submitted to HSA without the unredacted/ unedited reports from the primary reference agency will not qualify for the verification evaluation route. The applicant will be required to withdraw and resubmit the application via the abridged route if the applicant intends to pursue the application.

Primary reference agency	Documentary requirements
Health Canada	<ul style="list-style-type: none"> • Complete Clinical and Quality[#] assessment reports, including assessment on the Question & Answer documents between the Sponsor & Agency and all annexes • Assessment reports and/or documents pertaining to post-approval variations, if applicable

Primary reference agency	Documentary requirements
US FDA	<ul style="list-style-type: none"> • Complete Clinical and Quality[#] assessment reports, including assessment on the Question & Answer documents between the Sponsor & Agency and all annexes* • Assessment reports and/or documents pertaining to post-approval variations, if applicable <p><i>* Companies who face difficulties in obtaining the unredacted reports can submit the “FDA Sponsor’s Authorization” (signed by the product’s Sponsor in the US) to HSA prior to the submission of the registration application, and HSA will help to facilitate the retrieval of the reports. The application should only be made after HSA receives the assessment reports from FDA. The unredacted assessment reports are pre-requisites at the point of making the application and the submission of the “FDA Sponsor’s Authorization” alone does not qualify the application for verification.</i></p>

Primary reference agency	Documentary requirements
UK MHRA	<ul style="list-style-type: none"> • Complete Clinical and Quality[#] assessment reports, including assessment on the Question & Answer documents between the Sponsor & Agency and all annexes[†] • Assessment reports and/or documents pertaining to post-approval variations, if applicable <p><i>† All assessment reports (interim and final) (e.g. Day 70, Day 120, Day 200, etc., according to the respective EU procedure), all question and answer documents, and all other relevant documents (e.g. comments from CMS for MRP/DCP) should be submitted in accordance with the respective EU procedure:</i></p> <ul style="list-style-type: none"> - National Procedure - Mutual Recognition Procedure [where UK MHRA acted as the Reference Member State (RMS)]. - Decentralised Procedure [where UK MHRA acted as the RMS].

Primary reference agency	Documentary requirements
EMA	<ul style="list-style-type: none"> • Complete Clinical and Quality[#] assessment reports, including assessment on the Question & Answer documents between the Sponsor & Agency and all annexes[‡] • Assessment reports and/or documents pertaining to post-approval variations, if applicable <p>[‡] All assessment reports (interim and final) (e.g. Day 80, Day 120, Day 150, Day 180, etc.), all question and answer documents, and all other relevant documents should be submitted in accordance with the EU Centralised Procedure.</p> <p>Companies who face difficulties in obtaining the unredacted reports can submit the EMA form for “Applicant’s Consent to Share Assessment and Inspection Documents with Non-European Union (EU) Regulatory Authorities” (signed by the product’s MAH in the EU) to HSA prior to the submission of the registration application, and HSA will help to facilitate the retrieval of the reports. The application should only be made after HSA receives the assessment reports from EMA. The unredacted assessment reports are pre-requisites at the point of making the application and the submission of the “Applicant’s Consent to Share Assessment and Inspection Documents with Non-European Union (EU) Regulatory Authorities” alone does not qualify the application for verification.</p>

Primary reference agency	Documentary requirements
TGA	<ul style="list-style-type: none"> • Complete Clinical assessment reports, including assessment on the Question & Answer documents between the Sponsor & Agency and all annexes • Complete Chemistry and Quality Control Assessment Report[#], including assessment on the Question & Answer documents between the Sponsor & Agency and all annexes • Delegate's overview • Pre-ACPM response • ACPM minutes • Assessment reports and/or documents pertaining to post-approval variations, if applicable

[#] If the drug substance section is submitted to the primary reference agency as a Drug Master File (DMF), the complete assessment report for the DMF, including the assessment on the Question & Answer (Q&A) documents between the DMF Holder & Agency and all annexes should be provided. Assessment reports, approval letters and/or documents pertaining to post-approval DMF updates should also be submitted, if applicable. Companies who face difficulties in obtaining the complete unredacted assessment report for the DMF (including the assessment on the Q&A documents) can submit the "DMF Holder's Authorization Form" (signed by the DMF Holder) to HSA prior to the submission of the registration application, and HSA will help to facilitate the retrieval of the reports. The application should only be made after HSA receives the assessment reports from the agency.

Administrative documents specific to the verification evaluation route that are required at the time of submission include:

- (a) Section 1.9 – Official approval letters, or equivalent documents, from the relevant reference drug regulatory agencies that certify the registration status of the drug product;
- (b) Section 1.13 – Official letter declaring that the application submitted to HSA or similar direction(s) of use, indication(s), dosing regimen(s) and/or patient

group(s) have not been rejected, withdrawn, approved via appeal process⁹, or pending deferral¹⁰ by any drug regulatory agency, with reasons in each case if applicable;

- (c) Section 1.14 – Official letter declaring that the Drug Master File provided is the same as that submitted to the primary reference agency, if applicable; and
- (d) Section 1.14 – Official letter declaring that all aspects of the product's quality intended for sale in Singapore are identical to that currently approved by the primary reference drug regulatory agency. This includes, but is not limited to, the formulation, site(s) of manufacture, release and shelf life specifications and primary packaging.

The technical documents required include:

- Quality documents:
 - From Sponsor:
 - Complete documents for both drug substance and drug product (ICH Module 3/ACTD Part II) as initially submitted to the primary reference agency;
 - Complete assessment reports including assessment on the Question & Answer documents between the Sponsor and primary reference agency, and other relevant supporting documents from the primary reference agency;
 - Questions and answers between the primary reference agency and Sponsor – the answers should include the supporting documents used in response to the questions;
 - All post-approval variations (if applicable) approved by the primary reference agency up to the time of submission to HSA, including the application letter for the variation, supporting documents for the variation, assessment report for the variation, questions and answers between the primary reference agency and Sponsor and the approval letter for the variation from the primary reference agency; and

⁹ Approval via appeal process includes, but is not limited to, the following: approval following negative opinion, approval following rejection, approval following non-approvable etc.

¹⁰ Deferral includes, but is not limited to, the following: non-approvable, approvable, conditional approval, conditional marketing authorisation, notice of compliance with conditions etc.

-
- Relevant documents required by HSA which have not been submitted to the primary reference agency, e.g. stability studies in accordance to ASEAN Stability Guidelines, etc.
 - From DMF Holder, if applicable:
 - The initial open and closed parts of the DMF submitted to the primary reference agency should be provided to HSA, together with a colour scanned copy of the Letter of Access;
 - Complete DMF assessment report including assessment on the Question & Answer documents between the DMF holder and the primary reference agency, and other relevant supporting documents from the primary reference agency;
 - Questions and answers between the primary reference agency and DMF Holder – the answers should include supporting documents used in response to the questions; and
 - All post-approval DMF updates (if applicable) approved by the primary reference agency up to the time of submission to HSA, including the application letter for the DMF update, supporting documents for the DMF update, assessment report for the DMF updates, questions and answers between the primary reference agency and Sponsor, and the approval letter for the DMF update from the primary reference agency.
 - a non-clinical overview; and
 - a clinical overview, summaries of clinical efficacy and clinical safety, synopses of relevant studies, a tabular listing of the clinical development programme and study reports of the pivotal studies (the tables and appendices to the pivotal study reports may be submitted upon request by HSA).

All of the data submitted to HSA must be the same as the data package submitted to the reference drug regulatory agencies. Differences between the dossier submitted to HSA and data reviewed by the reference drug regulatory agencies will not only delay the processing of the application, but may also lead to re-routing of the dossier to the abridged evaluation route if significant undisclosed differences have been discovered.

In the event that the chosen primary reference agency does not bear the most stringent indication(s), dosing regimen(s), patient group(s) and/or direction(s) of use among those approved by the reference drug regulatory agencies, a supplemental clinical assessment report from the reference drug regulatory agency that approved the most stringent indication(s), dosing regimen(s), patient group(s) and/or direction(s) of use is required. Reports from the public domain are acceptable. The proposed PI/PIL should be identical to that approved by this reference drug regulatory agency (with the exception of country-specific information).

CHAPTER D **GENERIC DRUG APPLICATION SUBMISSION**

This chapter applies to applications to register generic products.

A generic drug application applies to a therapeutic product that contains one or more chemical entities, and that is essentially the **same** with a current registered product with respect to its qualitative and quantitative composition of active ingredients, pharmaceutical dosage form and clinical indication.

Follow-on biologic products (also known as biosimilar products) are not eligible for a GDA and are required to be submitted via a NDA.

16 APPLICATION TYPES

There are two application types for a generic drug application:

GDA Generic Drug Application

GDA-1: For the first strength of a generic chemical product.

GDA-2: For subsequent strength(s) of the generic chemical product that has been registered or submitted as GDA-1. The product name and dosage form should be the same as that for the GDA-1.

In cases where multiple strengths of a generic product are submitted together, the strength of the product used in the BE study is considered as a GDA-1. The remaining strength(s) should be submitted as GDA-2.

16.1 Generic Product

A generic product must have the same qualitative and quantitative composition in active substances and be of the same pharmaceutical form as a currently registered product in Singapore (known as the 'Singapore reference product'). A generic product must demonstrate bioequivalence to the Singapore reference product via appropriate bioequivalence studies.

The generic product must fulfil the following criteria:

- (a) the generic product is the same pharmaceutical dosage form as the Singapore reference product. However, different conventional oral immediate-release dosage forms (i.e. tablets and capsules) are considered to be the same pharmaceutical form;
- (b) the route of administration of the generic product is the same as the Singapore reference product;
- (c) the conditions of use for the generic product fall within the directions for use (including indication(s), dosing regimen(s) and patient group(s)) for the Singapore reference product; and
- (d) the generic product is bioequivalent with the Singapore reference product.

16.2 Singapore Reference Product

The Singapore reference product must be a currently registered product that has been granted market authorisation based on the evaluation of the product's quality, efficacy and safety – i.e. a dossier with chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. If such a reference product is not registered in Singapore, then an alternate registered comparator product may be used if adequately justified (e.g. a registered generic therapeutic product widely used by local hospitals) by the applicant and agreed upon by HSA.

The generic product should contain the same active substance(s) and strength(s) and be the same pharmaceutical dosage form as the Singapore reference product.

For generic products containing a different salt, ester, ether, isomer, mixture of isomer, complex or derivative of the active substance compared to the Singapore reference product, applicants are required to submit data to demonstrate that the different form does **not** differ from the active substance in the Singapore reference product in terms of safety and/or efficacy.

Applicants are advised to search [HSA's Register of Therapeutic Products](#) to identify the Singapore reference product. Applicants are encouraged to contact HSA to

discuss the acceptability of a GDA if the generic product does not have a registered Singapore reference product of the same strength. In these instances, applicants should provide scientific justifications for HSA's consideration.

Applicants submitting GDAs should also refer to Appendix 10 for further details on product interchangeability and biowaiver requests.

17 EVALUATION ROUTES

There are three evaluation routes for a GDA: abridged, verification and verification-CECA evaluation routes. The eligibility criteria are different for each evaluation route. Applicants should be familiar with the criteria for each evaluation route because each route has different documentary requirements.

Figure 4 is a schematic diagram illustrating the evaluation routes for GDAs:

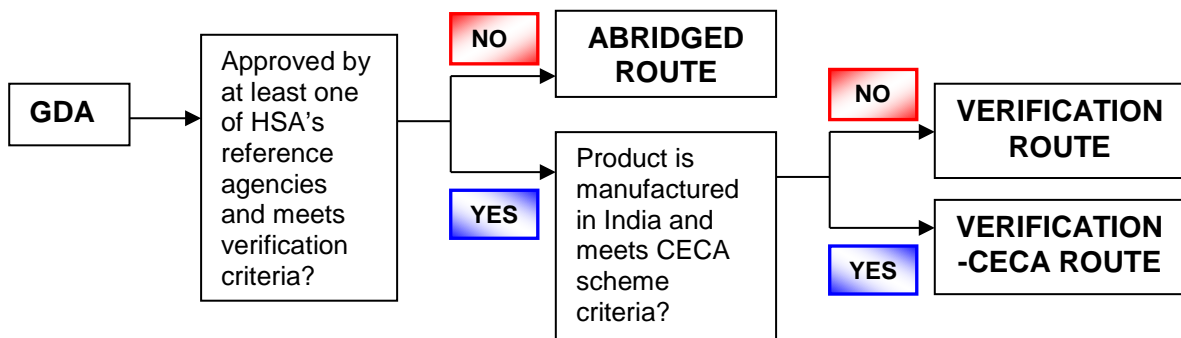


Figure 4 Schematic Diagram of Evaluation Routes for GDAs

17.1 Abridged Evaluation Route

Abridged evaluation applies to a product that has been approved by at least one drug regulatory agency at the time of submission.

17.2 Verification Evaluation Route

The verification evaluation route applies to a product that has been evaluated and approved by at least one of the following HSA's reference drug regulatory agencies:

-
- Australia Therapeutic Goods Administration (TGA);
 - Health Canada;
 - US Food and Drug Administration (FDA);
 - European Medicines Agency (EMA) **via the Centralised Procedure**; and
 - UK Medicines and Healthcare Products Regulatory Agency (UK MHRA) via
 - the national procedure; or
 - as the Reference Member State (RMS) via the Mutual Recognition Procedure or Decentralised Procedure.

However, approval by these reference drug regulatory agencies does not oblige HSA to approve the application.

Additional eligibility criteria for the verification route include:

- (a) The application must be submitted to HSA within two years from the date of approval by the chosen reference drug regulatory agency;
- (b) A declaration letter issued by the product owner/applicant must be provided stating that all aspects of the product's quality, including but not limited to the formulation, manufacturing site(s), release and shelf life specifications and primary packaging, are identical to that currently approved by the chosen reference drug regulatory agency at the time of submission. However, a different container closure system type (e.g. Alu/Alu blister vs. HDPE bottle) may be proposed to meet ASEAN stability requirements;
- (c) If a Drug Master File is submitted, then a separate declaration letter issued by the applicant must also be provided to state that the DMF submitted to HSA is identical to that submitted to the chosen reference drug regulatory agency;
- (d) The product and its intended use – i.e. indication(s), dosing regimen(s) and patient group(s) – have not been rejected, withdrawn, or approved via appeal process or are not pending deferral by a drug regulatory agency for efficacy and/or safety reasons; and,
- (e) The product has not been approved by the chosen reference drug regulatory agency via an accelerated/fast-track approval, approval under exceptional circumstances or an equivalent process.

The **chosen** reference drug regulatory agency is defined as the reference drug regulatory agency for which the qualifying supporting documents (as outlined in this guidance) will be submitted.

18 DOCUMENTARY REQUIREMENTS

Table 7 outlines the CTD Modules/Parts required for GDAs submitted under each evaluation route:

Table 7 Dossier Submission Requirements for a GDA

Documents	Location in		Module/Part required for		
	ICH CTD	ACTD	Abridged GDA	Verification GDA	Verification -CECA GDA
Administrative Documents and Product Information	Module 1	Part I	Yes	Yes <i>(Refer to section 18.5.2)</i>	Yes <i>(Refer to section 18.5.2)</i>
Common Technical Document Overview and Summaries	Module 2	<i>Incorporated into Part II</i>	QOS	QOS	QOS
Quality documents	Module 3	Part II	Yes	Yes <i>(Refer to section 18.5.2)</i>	Yes <i>(Refer to section 18.5.2)</i>
Non-clinical documents	Module 4	Part III	No	No	No
Clinical documents	Module 5	Part IV	BE studies or biowaiver justification may be	Yes <i>(same dataset as that)</i>	Yes <i>(same dataset as that)</i>

			inserted in this section	<i>submitted to RA)</i>	<i>submitted to RA)</i>
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18.1 Administrative Documents

The administrative documents relate to Module 1 of the ICH CTD or Part I of the ACTD and are applicable to the evaluation routes for GDAs. The following sections are to be submitted:

Cover Letter (to attach under CTD/PRISM section 1.2 - Introduction)

To include a cover letter stating the PRISM application number of the submission, the product name, and the number of CD/DVDs submitted in the application dossier.

Comprehensive Table of Contents (CTD/PRISM section 1.1)

The comprehensive table of contents is a complete list of **all** documents provided in the application dossier listed by Module/Part. The location of each document should be identified by the Module/Part number.

NOTE: Applicants must complete the relevant checklists found in Appendix 2A or Appendix 3A and attach the completed checklist under PRISM section 1.2

Introduction (CTD/PRISM section 1.2)

Applicants should give a concise summary of the application – for example, an overview of the bioequivalence study and the Singapore reference product used in support of the application.

Applicants should also justify the lack of certain documents within the dossier and deviation from the guidelines, if any.

Labelling, Package Insert and Patient Information Leaflet (CTD/PRISM section 1.4)

All proposed labels are to be submitted for registration. Applicants are required to provide the artwork/drafts of the proposed Singapore product labels, PI and/or PIL for the product. The clinical information in the proposed PI/PIL should be consistent with that currently approved for the Singapore reference product.

The submission of the proposed PI or PIL is dependent on the forensic classification of the product to be registered, as described in Table 8:

Table 8 Submission of Proposed PI or PIL According to Forensic Classification in Singapore

	Forensic Classification in Singapore		
	POM	P	GSL
Package Insert (PI), also known as prescribing information, SPC, or product monograph	Required	<i>Optional</i>	<i>Optional</i>
Patient Information Leaflet (PIL), also known as consumer medicine information (CMI)	<i>Optional, unless warranted</i>	Required	Required

One PI and/or PIL should be registered for each product application. If multiple manufacturing sites are proposed for registration, information for all sites should be included in one PI and/or PIL. If there are different strengths or dosage forms, one common PI/PIL for all strengths or dosage forms is encouraged. If separate PI/PILs are to be registered for different strengths or dosage forms, the content should be consistent across the PI/PILs, except for strength/dosage form-specific information.

All artwork and drafts should be legible. The draft artwork of the outer carton and inner/blister labels should be consistent with the format, design and colour that are to be printed. Separate labels must be submitted for each different pack size of the drug product.

Handwritten information is not acceptable, with the exception of statements such as 'batch number and expiry dates will be printed' or similar on the outer carton or inner/blister labels. Movable text boxes/pictures placed over other hidden information/text are also not acceptable.

The product labels, PI and/or PIL must be in English. If non-English text is included in the labelling, applicants must provide an official statement to declare that the non-English text is complete, accurate and unbiased information and is consistent with the English text.

Appendix 7 of this guidance contains specific details on the product labelling requirements for Singapore.

Approved SPC/PI/PIL (CTD/PRISM section 1.5)

In this section, the applicant should submit the approved SPC, PI and/or PIL from the drug regulatory agency that issued the proof of approval.

For applications submitted under the verification and verification-CECA evaluation routes, the SPC/PI/PIL approved by the chosen reference drug regulatory agency should be submitted.

The country from which the submitted SPC, PI and/or PIL originates should be appropriately indicated (e.g. in the document file name).

Assessment Report from Reference Agencies (CTD/PRISM section 1.6)

This section refers only to applications submitted under the verification or verification-CECA evaluation routes. Assessment reports and supporting documents issued by the chosen reference drug regulatory agency and inserted into this section must be unredacted and unedited. Applicants should refer to [section 18.5.2 Verification and Verification-CECA Evaluation Routes](#) for specific details on the required documents.

Description of Batch Numbering System (CTD/PRISM section 1.7)

Detailed information on the system of assigning unique codes to different production batches of the product should be provided to allow for batch identification. Where applicable, examples of the batch numbering system should be included to illustrate how the batch number enables identification.

Proof of Approval (CTD/PRISM sections 1.8, 1.9)

Proof of approval is not required for GDAs undergoing abridged evaluation for finished products manufactured (up to primary packaging) in Singapore.

For an abridged evaluation of an imported GDA, proof of approval from any drug regulatory agency is required. Proof of approval must come in the form of:

- an official approval letter, or equivalent document (e.g. Certificate of Pharmaceutical Product), which certifies the registration status of the drug product; and
- the SPC, PI and/or PIL approved by the drug regulatory agency that issued the approval letter.

For a verification or verification-CECA evaluation of a GDA, proof of approval from the chosen reference drug regulatory agency is required. Proof of approval must come in the form of:

- an official approval letter; and
- the SPC, PI and/or PIL approved by the drug regulatory agency that issued the approval letter.

If the SPC is in a non-English language, applicants should refer to [section 6.2.2 Language and Translation](#) of this guidance document for more information on acceptable translations.

Note that all aspects of the product's quality should be the same as those approved by the drug regulatory agency that issued the approval letter.

Certificate of Pharmaceutical Product (CPP) should be valid at the time of submission and should comply with WHO format (refer to [Model certificate of a pharmaceutical product](#)) It is not required for information such as the product formula, manufacturing sites, etc. to be reflected on the CPP, but if such information are present in the CPP, the information should be consistent with that proposed for the Singapore market. Note that CPPs that indicate that the product is not licensed in the exporting country (including scenario where the product is licensed for “solely for export only”) are not acceptable proof of approval.

Approval letters should either be an original copy or a certified true copy and in English. Applicants should refer to [sections 6.2.2 Language and Translation](#) and [6.2.3 Certifying Non-Original Documents](#) for more details. Reference to drug regulatory authority websites in the form of website screenshot and URL (for the website) for confirmation of the approval status of the products in that regulatory authority are acceptable, provided that the product's identity and product's ownership can be confirmed from that website.

HSA reserves the right to request for a Certificate of Pharmaceutical Product (CPP), if deemed appropriate.

If the brand name (trade name) of the product registered in the country which issued the proof of approval is different from that proposed in Singapore, the applicant is required to submit a declaration letter from the product owner to declare that both products marketed under the different brand names are **identical** in all aspects of quality, safety and efficacy except for the brand name.

Authorisation Letters (CTD/PRISM section 1.10)

All submitted authorisation letter(s) should be on the authorising company's (i.e. product owner's) letterhead, dated and signed by the designated authorised person in the company.

If the product owner is not the local applicant, manufacturer and/or batch releaser; or the product owner's address is different from that of the local applicant firm, manufacturer and/or batch releaser, then the following authorisation letter(s) must be submitted:

- (a) *from Product Owner to the Applicant (Company)* (1.10.1) – this letter authorises the local applicant to apply for and be the product registrant for a specific therapeutic product (product name to be stated as in PRISM) and be responsible for all matters pertaining to the registration of this product in Singapore.
- (b) *from Product Owner to Manufacturer* (1.10.2) – this letter authorises the specified manufacturer to produce, pack and/or label the drug product intended for Singapore. If there are multiple drug product manufacturers, then the

applicant may opt to submit one authorisation letter which clearly states all of the manufacturers (names and addresses) and their responsibilities relating to the drug product (such as the manufacturing operation of each manufacturer in relation to the product being submitted).

- (c) *from Product Owner to Batch Releaser (1.10.3)* – this letter authorises the specified company to batch release the drug product. If there are multiple sites responsible for the batch release of the product, then the applicant may opt to submit one authorisation letter which clearly states all of the batch releasers (names and addresses) and their responsibilities.

The applicant may also issue an authorisation letter to authorise the specified secondary packager located in Singapore to pack and/or label the drug product intended for Singapore.

Applicants are to ensure that all names and addresses in the authorisation letter(s) are consistent with the information provided in PRISM and the dossier. For manufacturers and batch releasers, the actual site address of the named company should be stated in the letter(s) – i.e. do not state the office address. Any discrepancy found will delay the registration process.

All authorisation letters should also state specific product details, including the product name, dosage form and strength as stated in the PRISM application form.

Applicants also have the option to combine the authorisation letters as stated above into one document, provided that all names, addresses and responsibilities are clearly stated.

GMP Certification/Proof of GMP Compliance (CTD/PRISM section 1.11)

Documentary evidence must be provided to certify that the manufacturer(s) complies with current applicable GMP standards. Applicants must submit a GMP certificate issued by a drug regulatory agency for all drug product manufacturing sites including, but not limited to, bulk product manufacturer(s), primary packer(s) and secondary packer(s). A CPP may be submitted *in lieu* of a GMP certificate provided that the manufacturer's name(s) and address(es) is(are) stated on the

CPP and the CPP states that the certifying authority conducts periodic inspection of the manufacturing plant in which the dosage form is produced. Applicants should note that the names and addresses of all manufacturers should be consistent throughout the application – i.e. GMP certificate, Letter of Authorisation, CTD section S.2.1 and P.3.1 and PRISM.

[EudraGMP](#), the database of the European Community of manufacturing authorisations and of certificates of good manufacturing practice, is an acceptable alternative proof of GMP compliance *in lieu* of a GMP certification. Applicants making reference to the EudraGMP as the proof of GMP compliance should provide a screen capture of the EudraGMP website for the specific finished product manufacturing site, as well as the URL to the website.

Certain accreditation documents/certificates issued by other drug regulatory agencies (for example, Japan/PMDA Accreditation Certificate of Foreign Drug Manufacturer, US/FDA Establishment Licence, Canada/Health Canada Establishment Licence) are not acceptable proof of GMP compliance.

NOTE: For applications submitted via the verification-CECA evaluation route, a valid GMP certificate and the latest inspection report as issued by the chosen reference drug regulatory agency must be submitted.

Proof of GMP compliance must be valid at the time of submission to HSA and must be in English. Applicants should refer to [section 6.2.2 Language and Translation](#).

If the submitted proof of GMP compliance is no longer valid or has less than 1 month's validity at the time of acceptance of the application for evaluation, HSA reserves the right to request for a commitment letter from the applicant to submit an updated and valid proof of GMP compliance by a specified date post-acceptance.

It should be noted that diluents used for reconstituting the drug product and are packaged together with the drug product will be considered as part of the final drug product. Thus, manufacturer(s) of the supplied diluent(s) must follow the same requirements applicable to the drug product, e.g. provide proof of GMP compliance.

For products manufactured in the USA or Canada, if the applicant is unable to obtain any proof of GMP compliance (in the form of a CPP or GMP certificate) from either US FDA/Health Canada or other drug regulatory agencies, the applicant is required to submit the latest Establishment Inspection Report (EIR) issued by US FDA or Inspection Exit Notice issued by Health Canada, and any other relevant supporting documents¹¹ as proof of GMP compliance. The applicant is also required to provide the following information if not found in the inspection reports:

- the last audited date by US FDA/Health Canada;
- the approved dosage forms ;
- any licensing conditions/restriction;
- the scope of inspection; and/or
- objective evidence and the date of a satisfactory close-out of the latest inspection conducted by US FDA/Health Canada.

For products manufactured in Switzerland, if the applicant is unable to obtain any proof of GMP compliance (in the form of a CPP or GMP certificate) from either SwissMedic or other drug regulatory agencies, the Manufacturer's Licence issued by SwissMedic is an acceptable documentary GMP evidence.

If the drug product is manufactured by a new overseas **drug product manufacturing site** not previously registered with HSA before 1st April 2004, a GMP Conformity Assessment will be conducted by HSA. Thus, when applicable, applicants must also submit the [application form to request for GMP Evidence Evaluation or for an Overseas GMP Audit](#) with the required documents to the Therapeutic Products Branch (as part of the product registration application) as stipulated in the [Guidance Notes on GMP Conformity Assessment of an Overseas Manufacturer](#).

In general, a GMP Conformity Assessment is applicable to each specific manufacturer, dosage form, manufacturing activities and applicant company. This

¹¹ Any other supporting document which declares GMP compliance of the manufacturing site in the US and signed by an official of the US FDA.

also includes contract manufacturers who perform certain manufacturing activities, such as terminal sterilisation of the drug product, mixing of excipient with drug substance (drug product intermediate), etc.

In general, applicant companies with active product registration that included the finished product manufacturer(s) performing the same manufacturing activities (excluding parametric release) for the same dosage form would not be required to undergo another GMP Conformity Assessment by HSA when they submit a new product application which included the same finished product manufacturer(s).

For drug product manufacturing sites that use parametric release (e.g. where a terminally sterilised product is released based on the review of manufacturing process data instead of sterility testing), a GMP Conformity Assessment is required for overseas drug product manufacturers. Eligibility criteria for such applications for overseas manufacturing sites are:

- a) Country of origin must be a PIC/S country
- b) Parametric release is approved by the local authority

If the above criteria are met, then approval letter and recent documentary evidence of approval status (e.g. GMP Certificate) for parametric release issued by the local authority should be provided. The manufacturing site and the product proposed for parametric release should be clearly stated on these documents.

For local manufacturing site that would like to apply for parametric release, applicants are advised to contact HSA prior to submission as pre-approval inspection is required.

HSA reserves the right to request for a GMP Conformity Assessment if deemed necessary, or to request for additional or updated documents as evidence of GMP compliance during the course of the registration process. HSA also reserves the right to conduct an audit of any overseas manufacturer irrespective of the documentary GMP evidence that is approved by HSA or any other PIC/S member authorities, if deemed appropriate.

If in doubt whether a GMP Conformity Assessment by HSA is required for the manufacturing sites included in the submission, applicants are encouraged to complete and submit applications to request for GMP Conformity Assessment with the product registration application, and HSA will advise accordingly whether the GMP Conformity Assessment would be required.

Patent Declaration (CTD/PRISM 1.12)

A signed and dated patent declaration form is required for each GDA. Applicants should refer to [section 3](#) for information on patent linkage and Appendix 1 for the Patent Declaration Form template.

Guiding notes on filling the Patent Declaration form are provided below:

- (a) Section 1 '*Applicant Particulars*' - state the name and address of the local company.
- (b) Section 2 '*Product Particulars*' - state the product name, name and strength of active ingredient and dosage form. All product particulars should be consistent with that stated in the product labels and other relevant documents as submitted in PRISM.
- (c) Section 3 '*Application Category*' - declare the patent category that the application falls under (with respect to a Singapore Patent as registered with IPOS).
- (d) Section 4 '*Information for Category A1 Applications*' - applicable if category A1 is selected in Section 3.
- (e) Section 5 '*Information for Category A2 Applications*' - applicable if category A2 is selected in Section 3. Check the box which is relevant and provide details of the patent in force.
- (f) Section 6 '*Information for Category A3 Applications*' - applicable if category A3 is selected in Section 3. Provide details of the patent in force.
- (g) Section 7 '*Information for Category B Applications*' - applicable if category B is selected in Section 3. Check the box which is relevant and provide details of the patent in force.
- (h) Section 8 '*Declaration*' - the patent declaration must be signed by the person authorised to make the declaration on behalf of the company named in Section 1. The authorised person is ordinarily an officer of the company such as

Company Director or Company Secretary as registered with ACRA, or equivalent. Evidence of such authorisation is to be submitted together with the declaration.

Evidence of authorisation for Section 8 can be in the form of:

- An ACRA printout¹² ([BizFile](#)) listing the Company Directors/Secretary;
- A resolution of board of directors;
- A resolution of a general meeting of the company; or
- An extract of the relevant portion of the company's articles of association.

Declaration forms must bear the signatures of the authorised person and the company stamp of the applicant.

NOTE: The applicant should ensure that the information provided in the patent declaration form and the evidence of authorisation are current at the point of application submission.

The patent declaration form needs to be submitted twice – at the time of submitting the application for registration and prior to the issuance of the regulatory decision for registration (upon request by HSA), if the dossier was deemed satisfactory with respect to the product's safety, efficacy and quality aspects.

Declaration on Rejection, Withdrawal and Deferral (CTD/PRISM section 1.13)

The document required for this section is a declaration letter issued by the product owner or applicant that states that the application submitted to HSA and the directions of use including indication(s), dosing regimen(s) and patient population(s)

- have not been rejected or withdrawn;
- have not been approved via an appeal process; and
- are not pending deferral

by any drug regulatory agency. If any of the above conditions apply to the application, details and reasons must be provided to HSA.

¹² The required information on the company's business profile should be obtained directly from ACRA's website ([BizFile](#)).

Declaration for GDA Verification and Verification-CECA (CTD/PRISM section 1.14)

This section applies only to the verification and verification-CECA evaluation routes.

A declaration letter issued by the product owner/applicant must be provided to state that all aspects of the product's quality are identical to that currently approved by the chosen reference drug regulatory agency at the time of submission. Quality aspects include, but are not limited to, formulation, manufacturing site(s), release and shelf life specifications, and primary packaging.

If a Drug Master File is submitted, then a separate declaration letter issued by the applicant must also be provided to state that the DMF submitted to HSA is identical to that submitted to the chosen reference drug regulatory agency.

Registration Status in Other Countries (CTD/PRISM section 1.15)

The registration status of the product in other countries should be entered into PRISM section 4.9 – refer to Appendix 17 of this document for further details.

In the event that the PRISM text space does not allow the input of the full details of the indication(s) and/or reason(s), a brief description may be entered. The full details should then be attached in softcopy (PDF) in PRISM section 7 (Supporting Attachments). The document should be in the format shown in [Table 6 in section 15.1](#) of this guidance document.

Confirmation of Reference Agency's Approval of Chemistry & Manufacturing Control (CMC) Aspects (CTD/ PRISM section 1.16)

For applications submitted under the abridged evaluation route and for which approval was obtained from at least one of HSA's reference agencies not more than 5 years before the date of submission to HSA, a colour scanned copy of the completed Dossier Clarification Supplement should be submitted in PRISM (refer to Appendix 18 *Confirmation of Quality Dossiers with Reference Agency's Approval* for more information).

18.2 CTD Overview and Summaries

The ICH or ASEAN Quality Overall Summary is to be inserted into Module 2 of the ICH CTD or into Part II, section B of the ACTD. This document can be submitted either in Word or PDF format.

18.3 Quality Documents

The quality documents relate to Module 3 of the ICH CTD or Part II of the ACTD. In addition to the ICH or ACTD technical content requirements, the following explanatory notes pertain to requirements specific to Singapore:

18.3.1 Body of Data – Drug Substance

The [ICH M4Q technical guideline](#) and [ASEAN Common Technical Requirements \(ACTR\)](#) provide details on the information to be included in the drug substance sections of an application dossier.

NOTE: If a drug product contains more than one drug substance, the information within Module 3.2.S (ICH CTD) or Part 2.S (ACTD) must be provided in its entirety for each drug substance.

All of the drug substance sections of the CTD – i.e. S1 to S7 – should be submitted in the application. If these sections are incomplete, then the dossier should make reference to a Drug Master File (DMF) or Certificate of Suitability of Monographs of the European Pharmacopoeia (CEP).

Because the drug product manufacturer is responsible for the quality control of the drug substance that is used in the drug product, applicants should note that the complete S section of the CTD dossier should be provided by the drug product manufacturer regardless of whether a DMF or a CEP has been submitted in support of a product application.

Drug Master File (DMF)

A Drug Master File (DMF) is a compilation of information on facilities, processes or components used in the manufacturing, processing, packaging and storing of a

drug that is submitted to the HSA. A DMF contains confidential information and is submitted solely at the discretion of the DMF holder.

A DMF is submitted in support of a therapeutic product application, and will be reviewed only in connection with the review of an application. As such, a separate approval will not be issued for a DMF.

Appendix 11 describes the DMF process and documentary requirements for DMF submission.

Certificates of Suitability (CEP)

A Certificate of Suitability is a document issued by the European Directorate for the Quality of Medicines and Healthcare (EDQM) that certifies the quality of a drug substance in compliance to the Ph. Eur. A CEP may be submitted *in lieu* of the CTD S Section or a DMF.

If reference is made to a CEP, the applicant should submit a copy of the duly authorised, valid CEP, including all annexes. A duly authorised CEP should contain the following information in the '*Declaration of Access*' section of the CEP:

- name of the Product Owner or local applicant;
- name of the product to be registered – it is recommended that the dosage form and strength(s) also be stated;
- signature and company stamp of the CEP holder; and
- date of authorisation.

The following additional requirements apply for CEP-based submissions:

- (a) If Ph. Eur. standard is claimed for the drug substance, the relevant CTDs should be submitted:
- (i) S.2.1;
 - (ii) S.4.1 and S.4.4 from both the drug substance and drug product manufacturers; and
 - (iii) S.6 and S.7 should be provided if the re-test period/shelf life is not stated on the CEP.

- (b) If other standards are claimed for the drug substance, the relevant CTDs should be submitted:
- (i) S.2.1;
 - (ii) S.4.1 to S.4.5 from both drug substance and drug product manufacturers; and
 - (iii) S.6 and S.7 should be provided if re-test period/shelf life is not stated on the CEP.

NOTE: HSA reserves the right to request for any additional information about the CEP-certified drug substance if it is deemed appropriate.

If there is a CEP for animal-derived material used in the drug product, the applicant may submit the CEP together with the documents stipulated in Annex 1- section 1.1 of Appendix 9 *Guideline on the Registration of Human Medicinal Products Containing Materials of Animal Origin*.

It is the applicant's responsibility to submit the latest CEP updates, with annexes, as soon as they are available from EDQM.

Control of Drug Substance (CTD section 3.2.S.4)

Batch analysis data should be provided by the drug substance and drug product manufacturers, and if available, from the same drug substance batches. Analytical results should be provided from a minimum of two batches from each proposed drug substance manufacturer and should be sufficient to support the specification(s) as well as to demonstrate consistency in manufacturing. The batches submitted should preferably be of production scale or at least pilot scale and should include the batch(es) used in the bioequivalence or biowaiver studies (where applicable).

Stability Data of Drug Substance (CTD section 3.2.S.7)

At the time of submission, the minimum stability data required are as follows:

- At least 12 months of long term data and 6 months of accelerated data from at least three primary batches of the drug substance;

- The batches should be at least pilot scale-sized and manufactured by a method that simulates the final commercial process.

If the drug substance is sourced from multiple sites, stability data from each site should be provided.

HSA may request for additional stability data if deemed necessary for the evaluation of the application.

18.3.2 Body of Data – Drug Product

The [ICH M4Q](#) technical guideline and [ACTR](#) also provide details on the information to be included in the drug product sections of an application dossier. For drug product intermediates and diluents, separate drug product sections should be submitted.

Pharmaceutical Development (CTD section 3.2.P.2)

Detailed descriptions and discussions, with relevant data, which relate to the development, and hence quality, of the drug product should be provided in the relevant dossier sections. Examples include, but are not limited to:

- polymorphism, solubility or particle size of the drug substance and its effect on the product's quality;
- a description and the results of the formulation development;
- the rationale for the choice of dissolution method and a discussion of its discriminatory nature, with data;
- compatibility of the container closure system with the product or preservative efficacy test results; and
- optimisation of the manufacturing process, with data.

Process Validation (CTD section 3.2.P.3.5)

The description, documentation and complete results of the validation studies on the manufacturing process should be provided in the dossier in this section. Particular care should be taken to ensure that the documents include critical processes for the manufacturing process: for example, blend uniformity validation for oral dosage forms and terminal sterilisation or aseptic filling for sterile products.

Applicants should refer to the [ASEAN Guidelines on Submission of Manufacturing Process Validation Data for Drug Registration](#) and the [ASEAN Guideline on Process Validation Q&A](#) for the minimum data requirements for process validation. Other relevant international guidelines may also be referred to as appropriate.

Where ranges of batch sizes are proposed, it should be demonstrated that variations in batch size would not adversely alter the characteristics of the finished product.

For drug product manufacturing sites that use parametric release (e.g. where a terminally sterilised product is released based on the review of manufacturing process data instead of sterility testing), a more detailed discussion with supporting data on the process validation of the specific product in the proposed pack size or fill volume should be provided. In addition, risk assessment for parametric release should be based on prior knowledge, consistency of performance of the steriliser, historical batch analysis data, risk of loading pattern/ container/ contamination from the environment to product sterility, re-processing plan and etc. A detailed discussion on the control strategy should also be provided. This includes but is not limited to, a tabulation of all validated critical process parameters and loading patterns, a description of the process and requirements for the release/rejection of a batch, bioburden monitoring and control program, the segregation of sterile products from non-sterile products and the routine maintenance/re-validation program for the steriliser.

Control of Excipients (CTD section 3.2.P.4)

This section refers to all excipients used in the drug product formulation, including ingredients used in capsule shells and film coatings. The specifications and analytical method(s) for each excipient should be described, including the validation of any in-house test method(s) if applicable.

Information on proprietary ingredients such as flavourings, colourants, coatings, perfumes and/or printing inks should be as detailed as possible. Applicants are advised not to use internal codes but instead to give commercial names for such ingredients. In cases where the formula of the proprietary ingredient is confidential,

only the total quantity of the proprietary ingredient present in the final product needs to be captured in PRISM. The formula of the proprietary ingredient should then be provided by the proprietary ingredient manufacturer directly to HSA. A declaration letter from the proprietary ingredient manufacturer should also be provided, indicating that they will inform HSA (via email to HSA_TP_Enquiry@hsa.gov.sg) should there be any change in the qualitative formulation of the proprietary ingredient.

A CoA for an excipient may be submitted *in lieu* of the excipient's specifications. If the standard claimed for an excipient is an officially recognised compendial standard, it is sufficient to state that the excipient is tested according to the requirements of that standard, rather than reproducing the specifications found in the officially recognised compendial monograph.

For excipients derived from animal sources, applicants should refer to Appendix 9 for more information. The checklist found in Annex 1 of Appendix 9 serves as a guide to these documentary requirements for submission. Applicants should note that the completed checklist in Annex 1 is to be submitted in CTD section 3.2.P.4.5 with the supporting documents submitted in ICH CTD section 3.2.A.2 or ACTD section Q.A.2.

For milk and certain milk derivatives such as lactose, as these excipients are generally considered non-infectious, a declaration from the supplier of the excipient stating that the milk is from healthy cows fit for human consumption and that no other potentially infectious ruminant-derived materials were used in the manufacturing process would be sufficient. This declaration is to be submitted in CTD section 3.2.P.4.5.

Control of Drug Product (CTD section 3.2.P.5)

The drug product's release and shelf-life specifications should be declared in section 3.2.P.5.1.

For the parametric release of a terminally sterilised product, the release specification and certificate of analysis should indicate that parametric release is

the method used for batch release. Additionally, sterility of the product is required to be demonstrated in the stability studies even if approval for parametric release has been granted.

Descriptions of all test methods with complete validation results of all in-house methods should be included in sections 3.2.P.5.2 and 3.2.P.5.3.

Descriptions (including size, origin and use) and test results of all relevant batches (e.g. pre-clinical, clinical, pilot and production batches) used to establish the specification and evaluate the consistency in manufacturing should be provided.

Batch analysis data and/or CoAs from three batches of the drug product should be provided in section 3.2.P.5.4.

The justification of the specifications (section 3.2.P.5.6) should be based on scientific knowledge and data collected during product development.

Container Closure System (CTD section 3.2.P.7)

Technical information about each component of the container closure system(s) used for the drug product should be included in the dossier. The technical information to be included in the dossier includes, but is not limited to, schematic diagrams, descriptions, specifications, analytical methods, CoAs and declarations of compliance to international standards.

Stability Data of Drug Product (CTD section 3.2.P.8)

Since 01 April 2014, HSA has implemented the [ASEAN Guideline on Stability Study of Drug Product \(the 'ASEAN guideline'\)](#), a guideline on the conduct of stability studies for drug products for the ASEAN region. Applicants should familiarise themselves with this guideline prior to submission.

At the time of submission of the application, the minimum stability data required are as follows:

- For **conventional dosage forms and stable drug substances**, at least 6 months of data under long term storage conditions and 6 months of data under

accelerated storage conditions on at least two primary batches of the drug product, as per the ASEAN guideline;

- For **critical dosage forms or unstable drug substances**, at least 12 months of data under long term storage conditions and 6 months of data under accelerated storage conditions on at least three primary batches of the drug product, as per the ASEAN guideline; and
- The primary batches should be manufactured by the same method(s) and packaged in the same container closure system as that proposed for Singapore.

It is recommended that the submitted stability data be specific for the sites proposed for registration in Singapore. For example, for a proposed product, if the drug substance is sourced from two different sites (e.g. sites A and B), the minimum stability data requirements for this drug product should include one set¹³ for the drug product with drug substance from site A and one set¹³ for the drug product with drug substance from site B – i.e. a total of six batches under long term conditions and six batches under accelerated conditions.

The table below illustrates the minimum requirement at the time of submission:

E.g. For drug substance sites A and B, drug product site Z.

Dataset submitted:
Conventional dosage forms and stable drug substances: 2 batches of A + Z <u>AND</u> 2 batches of B + Z
Critical dosage forms or unstable drug substances: 3 batches of A + Z <u>AND</u> 3 batches of B + Z

However, if the complete set of site-specific drug product stability data is not available at the time of submission of the application for chemical drug products, then the following conditions and requirements will apply:

(a) Multiple drug substance manufacturers:

¹³ 'One set' of stability data refers to the minimum number of batches required at the time of submission

If multiple drug substance manufacturers for one drug substance of the drug product are proposed for registration, then the following dataset is the minimum requirement at the time of submission:

- (i) The full CTD S section or CEP from each drug substance manufacturer;
- (ii) The same specification used by the drug product manufacturer for control of the drug substance (the 'DP-DS specification') from all of the proposed drug substance manufacturers, should encompass the following:
 - (A) The DP-DS specification captures all test parameters and limits from all of the proposed drug substance manufacturers, unless justified;
 - (B) If the same test parameters exist among the different drug substance manufacturers (e.g. assay, degradation products), then the limit should be aligned in the DP-DS specification; and
 - (C) If different test parameters exist among the drug substance manufacturers (e.g. residual solvents), then the limit should remain the same in the DP-DS specification.

The table below illustrates common DP-DS specification:

Drug Substance site A Drug Substance specification	Drug Substance site B Drug Substance specification	Drug Product site Z Drug Substance specification
Assay 98.0-102.0%	Assay 98.0-102.0%	Assay 98.0-102.0%
Impurity A NMT 0.2%	Impurity A NMT 0.2%	Impurity A NMT 0.2%
Methanol NMT 3000ppm		Methanol NMT 3000ppm ^a
	Isopropyl alcohol NMT 5000ppm	Isopropyl alcohol NMT 5000ppm ^b
^a Applicable for Drug Substance site A only		
^b Applicable for Drug Substance site B only		

- (iii) A minimum of one set¹³ of drug product stability data that represents all of the proposed drug substance manufacturers; and
- (iv) If the submitted stability dataset in (iii) does not represent all of the proposed drug substance manufacturers, then a commitment letter to conduct drug product stability studies for one batch of production scale, using the drug substance from each additional drug substance manufacturer that is not represented in (iii) is required.

The table below illustrates the possible submission options, which the applicant can choose one from at the time of submission:

E.g. For drug substance sites A and B (chemical drug substance only), drug product site Z.

Dataset submitted:	With commitment letter for:
Option 1: One set ¹³ of data using A+Z	1 production drug product batch for B+Z
Option 2: One set ¹³ of data using B+Z	1 production drug product batch for A+Z
Option 3: One set ¹³ of data using A+Z and B+Z	No commitment letter needed

Note: This approach does not apply to biological drug products – i.e. full drug substance site-specific drug product stability data are required at the time of submission.

(b) Multiple drug product manufacturers:

For biological drug products, the complete set of site-specific drug product stability data is required at the time of submission of the product application. For dossiers that are not able to meet this submission requirement, the applicant is

highly recommended to discuss the issues with HSA prior to submission in order to facilitate the registration process.

Conventional dosage forms and stable drug substances

For drug product of a **conventional dosage form and containing stable drug substance(s)**, if multiple drug product manufacturers for the drug product are proposed for registration, then the following dataset is the minimum requirement at the time of submission:

- (i) Drug product stability batches from each proposed drug product manufacturer should be provided; and
- (ii) The number of batches from each proposed drug product manufacturer must meet the submission requirement i.e. 2 batches of drug product with:
 - At minimum of 6 months of stability data under long term storage conditions and
 - 6 months of stability data under accelerated storage conditions, as per the ASEAN guideline

For drug product of a **conventional dosage form and containing stable drug substance(s)**, if a drug product manufacturer has manufactured development or pilot drug product batches but is not intended for registration, then the development/pilot drug product batches may be submitted in support of the proposed shelf-life and storage condition if the following dataset is submitted at the time of submission:

- (i) The complete CTD P.3 section (process validation to be submitted, if available) from the development/pilot drug product manufacturing site;
- (ii) Batch analyses or certificates of analysis (CTD P5.4) of the stability batches from the development/pilot manufacturing site;
- (iii) Two (2) batches of a minimum of 6 months of stability data from the development/pilot manufacturing site, as per the ASEAN guideline;
- (iv) Two (2) batches of a minimum of 6 months of stability data from the proposed drug product manufacturing site; and
- (v) A commitment to provide the completed stability studies (up to the proposed shelf-life) from the proposed drug product manufacturing site.

Critical dosage forms or unstable drug substances

For drug product of a **critical dosage form or containing unstable drug substances**, if multiple drug product manufacturers for the drug product are proposed for registration, then the following dataset is the minimum requirement at the time of submission:

- (i) Drug product stability batches from each proposed drug product manufacturer should be provided; and
- (ii) The number of batches from each proposed drug product manufacturer must meet the submission requirement i.e. 3 batches of drug product with:
 - A minimum of 12 months of stability data from one of the drug product manufacturer; and
 - A minimum of 6 months of stability data from the other drug product manufacturer(s).

For drug product of a **critical dosage form or containing unstable drug substances**, if a drug product manufacturer has manufactured development or pilot drug product batches but is not intended for registration, then the development/pilot drug product batches may be submitted in support of the proposed shelf-life and storage condition if the following dataset is submitted at the time of submission:

- (i) The complete CTD P.3 section (process validation to be submitted, if available) from the development/pilot drug product manufacturing site;
- (ii) Batch analyses or certificates of analysis (CTD P5.4) of the stability batches from the development/pilot manufacturing site;
- (iii) Three (3) batches of a minimum of 12 months of stability data from the development/pilot manufacturing site, as per the ASEAN guideline;
- (iv) Three (3) batches of a minimum of 6 months of stability data from the proposed drug product manufacturing site; and
- (v) A commitment to provide the completed stability studies (up to the proposed shelf-life) from the proposed drug product manufacturing site.

The table below illustrates the possible submission options, which the applicant can choose one from at the time of submission:

E.g. For drug substance site A, drug product sites Y and Z.

	Dataset submitted:
<u>GDA</u> (Conventional dosage forms and stable drug substances)	<u>Option 1:</u> 2 batches of a minimum 6 months stability data from one of the proposed commercial DP site (A+Y) AND 2 batches of a minimum 6 months stability data from the other proposed commercial DP site (A+Z)
	<u>Option 2:</u> 2 batches of a minimum 6 months stability data from developmental/ pilot DP site (A+Y) AND 2 batches of a minimum 6 months stability data from the proposed commercial DP site (A+Z)
<u>GDA</u> (Critical dosage forms or unstable drug substances)	<u>Option 1:</u> 3 batches of a minimum 12 months stability data from one of the proposed commercial DP site (A+Y) AND 3 batches of a minimum 6 months stability data from the other proposed commercial DP site (A+Z)
	<u>Option 2:</u> 3 batches of a minimum 12 months stability data from developmental/ pilot DP site (A+Y) AND

	3 batches of a minimum 6 months stability data from the proposed commercial DP site (A+Z)
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(c) Multiple drug substance and drug product manufacturers:

If multiple drug substance and drug product manufacturers are proposed for registration, then the dataset required at the time of submission will combine the requirements in (a) and (b) above.

The tables below illustrate the possible submission options, which Applicant can choose one from at the time of submission:

E.g. For drug substance sites A and B, drug product sites Y and Z for GDA of conventional dosage form and stable drug substance

Option 1:		No. of batches		Option 2:		No. of batches	
Site	Drug Product Site Y	Drug Product Site Z	Site	Drug Product Site Y	Drug Product Site Z		
Drug Substance Site A	1	1	Drug Substance Site A	2	0		
Drug Substance Site B	1	1	Drug Substance Site B	0	2		

Option 3:		No. of batches	
Site	Drug Product Site Y	Drug Product Site Z	
Drug Substance Site A	2	2	

Drug Substance Site B	0*	0*
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* Not all drug substance sites are represented; thus, a commitment to conduct stability on one production drug product batch (from either site Y or Z) using drug substance site B is required at time of submission.

Note: A minimum of 6 months of stability data for batches manufactured at Y and Z.

E.g. For drug substance sites A and B, drug product sites Y and Z for GDA of critical dosage form or unstable drug substance

Option 1:	No. of batches	
Site	Drug Product Site Y	Drug Product Site Z
Drug Substance Site A	2	3
Drug Substance Site B	1	0

Option 2:	No. of batches	
Site	Drug Product Site Y	Drug Product Site Z
Drug Substance site A	3	0
Drug Substance Site B	0	3

Option 3:	No. of batches	
Site	Drug Product Site Y	Drug Product Site Z
Drug Substance Site A	0	1
Drug Substance Site B	3	2

Option 4:	No. of batches	
Site	Drug Product Site Y	Drug Product Site Z
Drug Substance Site A	3	3
Drug Substance Site B	0*	0*

** Not all drug substance sites are represented; thus, a commitment to conduct stability on one production drug product batch (from either site Y or Z) using drug substance site B is required at time of submission*

Note: A minimum of 12 months of stability data for batches manufactured at Y, and 6 months of stability data for batches manufactured at Z.

OR

A minimum of 6 months of stability data for batches manufactured at Y, and 12 months of stability data for batches manufactured at Z.

(d) Multiple primary packagers:

If multiple primary packaging sites for the same container closure system are proposed for registration, then the following dataset is the minimum requirement at the time of submission:

- (i) A minimum of one set¹³ of stability data from one of the primary packaging sites;
- (ii) Transport validation of the bulk product to the other proposed primary packaging site(s), unless justification is provided; and
- (iii) A minimum of one set¹³ of 6 months of stability data from the other primary packaging site(s) with a commitment to provide the data upon completion of the stability study.

(e) Drug product stability batch(es) using development or pilot drug substance batches:

If the submitted stability dataset (one set¹³) uses development or pilot drug substance batches, the stability dataset may be submitted in support of the proposed shelf-life and storage condition if the following dataset is submitted at the time of submission:

(i) For drug product of a **conventional dosage form and containing stable drug substance(s)**:

- (A) CTD S section (S2.2, S3.1, S3.2, S4.1 and S4.4) from the development/pilot drug product manufacturing site;

- (B) Two (2) batches of a minimum of 6 months of stability data using drug substance manufactured from developmental or pilot drug substance site;
 - (C) A commitment letter to conduct 2 batches of long term and accelerated stability studies using drug substance manufactured from the proposed drug substance site(s), and report if any results fall outside shelf-life specifications (with proposed action) or when requested.
 - (D) Prior to approval: To provide a minimum of 6 months of stability data as committed in (C).
- (ii) For drug product of a **critical dosage form or containing unstable drug substances**:
- (A) CTD S section (S2.2, S3.1, S3.2, S4.1 and S4.4) from the development/pilot drug product manufacturing site;
 - (B) Three (3) batches of a minimum of 12 months of stability data using drug substance manufactured from developmental or pilot drug substance site;
 - (C) A commitment letter to conduct 3 batches of long term and accelerated stability studies using drug substance manufactured from the proposed drug substance site(s), and report if any results fall outside shelf-life specifications (with proposed action) or when requested.
 - (D) Prior to approval: To provide a minimum of 6 months of stability data as committed in (C).

Product Interchangeability – Bioequivalence (CTD section 3.2.P.9.1)

Since 01 April 2004, *in vivo* bioequivalence (BE) data are required for Prescription Only Medicines (POM) in oral solid dosage forms.

GDA-2 applications will also require BE data if the application is for a POM in an oral solid dosage form, even if the first strength (GDA-1) application was submitted to HSA before 01 April 2004.

Applicants should be familiar with Appendix 10 *Product Interchangeability and Biowaiver Request for Chemical Generic Drug Applications*.

Applicants should ensure that the submitted BE study is complete, including all appendices and data, according to the relevant guidelines. Examples of information to be included in the report are:

- (a) Signature of the Principal Investigator to attest the authenticity of the report;
- (b) Audit certificate(s);
- (c) BE site inspection report from a national regulatory agency or WHO, if available;
- (d) Approval letter(s) from the Institutional Review Board/Independent Ethics Committee and the appropriate drug regulatory agency;
- (e) Information about the reference and test products, such as the product name, strength, dosage form, batch number, manufacturing site, batch size of the test product, etc.;
- (f) Certificates of Analysis of the reference and test products used in the BE study, including the batch size of the test product and manufacturing/expiry date of both products (where applicable);
- (g) Bioanalytical study report and description of the bioanalytical method validation; and
- (h) A signed statement confirming that the test product used in the BE study is the same formulation and is manufactured by the same process as that submitted for registration.

Applicants should also provide a copy of the product labels (e.g. outer carton, product insert) of the reference product used in the BE study for verification purposes.

It is highly recommended that the generic or test product used in the BE study be the same as the drug product submitted for registration in Singapore. If this cannot be fulfilled, then applicants should refer to Appendix 10 *Product Interchangeability and Biowaiver Request for Chemical Generic Drug Applications* for more information regarding eligibility and documentary requirements.

In instances when the reference product used in the BE study is not the Singapore reference product, if the criteria listed in section 2 of Appendix 10 are fulfilled, then the following additional documents must be submitted in support of the application:

- (a) A comparative table that lists the qualitative composition of both the BE and Singapore reference products;
- (b) Comparative dissolution profiles between the BE and Singapore reference products; and
- (c) Comparative dissolution profiles between the BE test and Singapore reference products.

For Biopharmaceutics Classification System (BCS)-based biowaiver applications, justifications and relevant supporting documents should also be included under section 3.2.P.9.

Product Interchangeability – Comparative Dissolution Profile (CTD section 3.2.P.9.2)

Comparative dissolution profile data between the generic product and the Singapore reference product should be submitted in support of the following GDAs:

- POMs (immediate and modified release oral solid dosage forms); and
- P or GSL medicines (modified release oral solid dosage forms only).

For POMs supported by BE study data, the following additional comparative dissolution profile data should be submitted (applicable only when the BE reference product is not the Singapore reference product):

- (a) Between the reference and test products used in the BE study; and
- (b) Between the BE and Singapore reference products.

Applicants should also provide a copy of the product labels (e.g. outer carton, product insert) of the BE and Singapore reference products used in the comparative dissolution profile testing for verification purposes.

When a generic product is to be marketed in several strengths, applicants should refer to Section 3 of Appendix 10 *Product Interchangeability and Biowaiver Request for Chemical Generic Drug Applications* for more information on comparative dissolution profile testing requirements.

For BCS-based biowaiver applications, justifications and relevant supporting documents should also be included under section 3.2.P.9.

Applicants should be familiar with Appendix 10 *Product Interchangeability and Biowaiver Request for Chemical Generic Drug Applications*.

HSA reserves the right to request for any additional information required to determine the product interchangeability of the generic product to the Singapore reference product.

18.4 Non-clinical and Clinical Documents

Generally, non-clinical (animal) and clinical (human) data are not required to be included in a GDA. Instead, the data demonstrating the generic product's interchangeability with the Singapore reference product, e.g. *in vivo* BE and comparative dissolution studies, are required for submission.

Documentary requirements for establishing product interchangeability (including BCS-based biowaiver applications) can be found in Appendix 10 *Product Interchangeability and Biowaiver Request for Chemical Generic Drug Applications*.

Where required, HSA may request for RMPs to be submitted on a case-by-case basis for GDAs, following the evaluation of the safety profile of the product described in the product application. Guidance on RMP submission requirements can be found in Appendix 16 *Guideline on the Submission of Risk Management Plan Documents*.

18.5 Specific documentary requirements for each evaluation route

18.5.1 Abridged Evaluation Route

All aspects of the product's quality which include, but are not limited to, the formulation, site(s) of manufacture, release and shelf life specifications and primary packaging should be the same as that approved by the drug regulatory agency that issued the proof of approval.

The technical documents required include:

- complete quality documents for both the drug substance and drug product; and
- BE studies or justifications for applying a biowaiver, where applicable.

18.5.2 Verification and Verification-CECA Evaluation Routes

The complete assessment report and other relevant supporting documents from the chosen reference drug regulatory agency must be submitted, as tabulated below.

The assessment reports must be unredacted or unedited, and should include details of imposed licensing conditions, final product labelling, chemistry and clinical reviews, and other information in relation to the product's approval. Reports obtained from the public domain are deemed unacceptable.

Applications submitted to HSA without the unredacted/ unedited reports from the primary reference agency will not qualify for the verification evaluation route. The applicant will be required to withdraw and resubmit the application via the abridged route if the applicant intends to pursue the application.

Reference agency	Documentary requirements
Health Canada	<ul style="list-style-type: none"> • Complete Clinical and Quality[#] assessment reports, including assessment on the Question & Answer documents between the Sponsor & Agency and all annexes • Assessment reports and/or documents pertaining to post-approval variations, if applicable

Reference agency	Documentary requirements
US FDA	<ul style="list-style-type: none"> • Complete Clinical and Quality[#] assessment reports, including assessment on the Question & Answer documents between the Sponsor & Agency and all annexes* • Assessment reports and/or documents pertaining to post-approval variations, if applicable <p><i>* Companies who face difficulties in obtaining the unredacted reports can submit the “FDA Sponsor’s Authorization” (signed by the product’s Sponsor in the US) to HSA prior to the submission of the registration application, and HSA will help to facilitate the retrieval of the reports. The application should only be made after HSA receives the assessment reports from FDA. The unredacted assessment reports are pre-requisites at the point of making the application and the submission of the “FDA Sponsor’s Authorization” alone does not qualify the application for verification.</i></p>
UK MHRA	<ul style="list-style-type: none"> • Complete Clinical and Quality[#] assessment reports, including assessment on the Question & Answer documents between the Sponsor & Agency and all annexes[†] • Assessment reports and/or documents pertaining to post-approval variations, if applicable <p><i>† All assessment reports (interim and final) (e.g. Day 70, Day 120, Day 200, etc., according to the respective EU procedure), all question and answer documents, and all other relevant documents (e.g. comments from CMS for MRP/DCP) should be submitted in accordance with the respective EU procedure:</i></p> <ul style="list-style-type: none"> - National Procedure - Mutual Recognition Procedure [where UK MHRA acted as the Reference Member State (RMS)]. - Decentralised Procedure [where UK MHRA acted as the RMS]

Reference agency	Documentary requirements
EMA	<ul style="list-style-type: none"> • Complete Clinical and Quality[#] assessment reports, including assessment on the Question & Answer documents between the Sponsor & Agency and all annexes[‡] • Assessment reports and/or documents pertaining to post-approval variations, if applicable <p><i>[‡] All assessment reports (interim and final) (e.g. Day 80, Day 120, Day 150, Day 180, etc.), all question and answer documents, and all other relevant documents should be submitted in accordance with the EU Centralised Procedure.</i></p> <p><i>Companies who face difficulties in obtaining the unredacted reports can submit the EMA form for “Applicant’s Consent to Share Assessment and Inspection Documents with Non-European Union (EU) Regulatory Authorities” (signed by the product’s MAH in the EU) to HSA prior to the submission of the registration application, and HSA will help to facilitate the retrieval of the reports. The application should only be made after HSA receives the assessment reports from EMA. The unredacted assessment reports are pre-requisites at the point of making the application and the submission of the “Applicant’s Consent to Share Assessment and Inspection Documents with Non-European Union (EU) Regulatory Authorities” alone does not qualify the application for verification.</i></p>
TGA	<ul style="list-style-type: none"> • Complete Clinical assessment reports, including assessment on the Question & Answer documents between the Sponsor & Agency and all annexes • Complete Chemistry and Quality Control Assessment Report[#], including assessment on the Question & Answer documents between the Sponsor & Agency and all annexes • Assessment reports and/or documents pertaining to post-approval variations, if applicable

If the drug substance section is submitted to the chosen reference agency as a Drug Master File (DMF), the complete assessment report of the DMF, including assessment on the Question & Answer documents between the DMF Holder & Agency and all annexes should be provided. Assessment reports, approval letters and/or documents pertaining to post-approval DMF updates should also be submitted, if applicable. Companies who face difficulties in obtaining the complete unredacted assessment report for the DMF (including assessment on the Q&A documents) can submit the “DMF Holder’s Authorization Form” (signed by the DMF Holder) to HSA prior to the submission of the registration application, and HSA will help to facilitate the retrieval of the reports. The application should only be made after HSA receives the assessment reports from the agency.

Administrative documents specific to the verification and verification-CECA evaluation routes that are required at the time of submission include:

- (a) Section 1.4.3/1.4.4 – the proposed PI or PIL should be aligned to the currently-registered Singapore reference product PI or PIL;
- (b) Section 1.9 – Official approval letter from the chosen reference drug regulatory agency that certify the registration status of the drug product;
- (c) Section 1.13 – Official letter issued by the applicant or product owner declaring that the application submitted to HSA or similar direction(s) of use, indication(s), dosing regimen(s) and/or patient group(s) have not been rejected, withdrawn, approved via appeal process¹⁴, or pending deferral¹⁵ by any drug regulatory agency, with reasons in each case if applicable;
- (d) Section 1.14 – Official letter issued by the applicant or product owner declaring that the Drug Master File provided is identical to that submitted to the chosen reference drug regulatory agency, if applicable; and
- (e) Section 1.14 – Official letter from the applicant or product owner declaring that all aspects of the product’s quality intended for sale in Singapore are identical to that currently approved by the chosen reference drug regulatory agency. This includes, but is not limited to, the formulation, site(s) of manufacture, release and shelf life specifications and primary packaging.

¹⁴ Approval via appeal process includes, but is not limited to, the following: approval following negative opinion, approval following rejection, approval following non-approvable etc.

¹⁵ Deferral includes, but is not limited to, the following: non-approvable, approvable, conditional approval, conditional marketing authorisation, notice of compliance with conditions etc.

Specifically for the verification-CECA evaluation route, a valid GMP certificate and the latest GMP inspection report as issued by the reference drug regulatory agency must be submitted.

The technical documents required include:

- Quality documents:
 - From Sponsor:
 - Complete documents for both drug substance and drug product (ICH Module 3/CTD Part II) as initially submitted to the chosen reference drug regulatory agency;
 - Complete assessment reports including assessment on the Question & Answer documents between the Sponsor and chosen reference drug regulatory agency, and other relevant supporting documents from the chosen reference drug regulatory agency;
 - Questions and answers between the chosen reference drug regulatory agency and Sponsor – the answers should include supporting documents used in response to the questions;
 - All post-approval variations (if applicable) approved by the chosen reference drug regulatory agency up to the time of submission to HSA, including the application letter for the variation, supporting documents for the variation, assessment report for the variation, questions and answers between the chosen reference drug regulatory agency and Sponsor, and the approval letter for the variation from the chosen reference drug regulatory agency; and
 - Relevant documents required by HSA which have not been submitted to the chosen reference drug regulatory agency, e.g. stability studies in accordance to ASEAN Stability Guidelines, comparative dissolution studies, etc.
 - From DMF Holder, if applicable:
 - The initial open and closed parts of the DMF submitted to the chosen reference drug regulatory agency should be provided to HSA, together with a colour scanned copy of the Letter of Access;
 - Complete DMF assessment report including assessment on the Question & Answer documents between the DMF holder and the

- chosen reference drug regulatory agency, and other relevant supporting documents from the chosen reference drug regulatory agency;
- Questions and answers between the chosen reference drug regulatory agency and DMF Holder – the answers should include supporting documents used in response to the questions; and
 - All post-approval DMF updates (if applicable) approved by the chosen reference drug regulatory agency up to the time of submission to HSA, including the application letter for the DMF update, supporting documents for the DMF update, assessment report for the DMF updates, questions and answers between the chosen reference drug regulatory agency and Sponsor, and the approval letter for the DMF update from the reference drug regulatory agency.
- All clinical documents, such as BE studies or justification for biowaiver, as initially submitted to the chosen reference drug regulatory agency with all questions and answers, including supporting documents, between the reference drug regulatory agency and Sponsor; and
 - Any additional documents to demonstrate product interchangeability with the Singapore reference product as described in [section 18.3.2 Body of Data – Drug Product](#), where applicable.

Applicants are reminded that generic products applied through the verification and verification-CECA evaluation routes must still demonstrate product interchangeability to the Singapore reference product.

Data submitted to HSA must be the same as the data package submitted to the reference regulatory agencies. Differences between the dossier submitted to HSA and data reviewed by the reference drug regulatory agencies will not only delay the processing of the application, but may also lead to re-routing of the dossier to the abridged evaluation route if significant undisclosed differences are discovered.

In addition, the BE test product must be manufactured at the same drug substance and drug product manufacturing sites by the same manufacturing processes as submitted in the GDA application dossier.

18.6 Documentary Requirements for Second Brand Registration of Chemical Therapeutic Products

18.6.1 Definition

A second brand product refers to a chemical drug product which is identical to a registered (original) drug product in all aspects of quality, safety and efficacy at the time of its submission for market authorisation and is submitted by the same product registrant of the original drug product.

18.6.2 Documentary Requirements

18.6.2.1 *Administrative*

A complete set of administrative documents as per [section 18.1 Administrative documents](#) has to be submitted. In addition, a declaration that the second brand product is identical to the original drug product in terms of quality, safety and efficacy is required.

18.6.2.2 *Quality*

A complete set of quality documents as per [sections 18.2 CTD overview and summaries](#) and [18.3 Quality documents](#) has to be submitted. In addition, a comparative table of each CTD section between the second brand and original drug products is required and all differences between these two dossiers should be stated. The impact of these differences (if any) should generally be justified by the approval or submission of minor variation application - MIV (to state application number) to the original product dossier (see [Chapter H – Minor Variation \(MIV\) Application Submission](#)).

During the evaluation stage, if MIV has not been submitted for these differences to the original drug product dossier, then a MIV-2 application will be requested to update the original product dossier. A stop-clock will be imposed on the second brand product application until the update is completed. Product registrant is advised to file MIV for the update of these differences prior to submission to avoid any delay in the review process of the second brand product.

Submission of BE studies are generally not required for second brand product applications if the original product was granted marketing authorisation based on the evaluation of the product's quality, safety and efficacy. However if the original product was registered as a generic drug product before 01 April 2004, prior to the implementation of BE requirements, the current BE requirements will apply to the second brand product.

CHAPTER E BIOSIMILAR PRODUCT APPLICATION SUBMISSION

This chapter applies to new drug applications for biosimilar products.

A biosimilar product is a biological therapeutic product demonstrated to be similar, in physicochemical characteristics, biological activity, safety and efficacy to an existing registered biological product.

Applicants submitting applications to register biosimilar products must be familiar with the responsibilities of managing these products throughout their life cycle. Thus, it is recommended to refer to Appendix 15 *Guidance on Registration of Biosimilar Products* or [HSA's website](#) for more information.

This chapter serves to provide additional guidance on submission of biosimilar products.

19 APPLICATION TYPES

Biosimilar products are eligible for the NDA-2 and NDA-3 application types. When selecting the Product Type in PRISM section 3.2, select '*Biological Drug*'.

NDA New Drug Application

NDA-1: **Not** applicable to biosimilar products.

NDA-2: For the first strength of a biosimilar product with the same dosage form and route of administration as the Singapore reference biological product.

NDA-3: For subsequent strength(s) of a biosimilar product that has been registered or has been submitted as an NDA-2. The product name, dosage form, indication, dosing regimen and patient population should be the same as that for the NDA-2.

19.1 Biosimilar Product

A biosimilar product is intended to be similar in terms of quality, safety and efficacy to a registered biological product (reference biological product) for which there is substantial evidence of safety and efficacy.

Applicants are advised to search [HSA's Register of Therapeutic Products](#) to identify the Singapore registered biological product (Singapore reference biological product; see [section 19.2](#) below).

The standard generic approach of bioequivalence demonstration with reference to a chemically-derived drug product is scientifically inappropriate for biosimilar product applications since biological drugs are much more complex in their structure and inherent properties as compared to chemically-derived drugs. The biosimilar product approach, based on comparability (demonstration of similarity), should be followed.

The development of a biosimilar product involves stepwise comparability exercises starting with the comparison of the quality characteristics of the biosimilar product and the reference biological product. The demonstration of similarity in terms of quality is a prerequisite for the reduction of the non-clinical and clinical dataset required for registration. However, if relevant differences are found in the quality, non-clinical and/or clinical data, the product is unlikely to qualify as a biosimilar product and a more extensive non-clinical and clinical dataset may be required to support registration.

19.2 Singapore Reference Biological Product

The following are considerations for the choice of a biological reference product:

- The reference product should be a biological therapeutic product that is currently registered in Singapore (hereinafter known as '*Singapore reference biological product*'). A registered biosimilar product cannot be used as a reference product.
- The active substance(s) of the biosimilar product and the Singapore reference biological product should be similar in molecular and biological terms;

- The pharmaceutical form, strength and route of administration of the biosimilar product should be the same as the Singapore reference biological product. Any differences will require additional comparability assessment data and have to be justified by appropriate studies; and
- The conditions of use for the biosimilar product must fall within the directions for use (including indication(s), dosing regimen(s) and patient group(s)) of the Singapore reference biological product.

A biological product with no suitable Singapore reference biological product will not qualify for registration as a biosimilar product in Singapore.

20 EVALUATION ROUTES

A biosimilar product is only eligible for the abridged evaluation route. The product must have been approved by at least one of the following reference drug regulatory agencies: EU EMA, Australia TGA, UK MHRA, US FDA and Health Canada.

21 DOCUMENTARY REQUIREMENTS

Table 9 outlines the CTD Modules/Parts required for NDAs submitted for registration of a biosimilar product.

Table 9 Dossier Submission Requirements for Biosimilar Products

Documents	Location in		Module/Part required for
	ICH CTD	ACTD	Biosimilar product
Administrative Documents	Module 1	Part I	Yes
Common Technical Document Overview and Summaries	Module 2	<i>Incorporated in Parts II, III and IV</i>	Yes
Quality documents	Module 3	Part II	Complete quality module including comparability studies

Non-clinical documents	Module 4	Part III	Complete non-clinical module* including comparability studies
Clinical documents	Module 5	Part IV	Complete clinical module* including comparability studies

*The non-clinical and clinical dataset may be reduced based on criteria under [section 21.4](#)

Applicants are advised to refer to the Appendix 15 *Guidance on Registration of Biosimilar Products* for detailed information on the complete requirements for registering a biosimilar product.

21.1 Administrative Documents

The administrative documents of the application dossier for biosimilar products is the same as that described in [section 15.1 Administrative Documents](#) in Chapter C *New Drug Application Submission*.

21.2 CTD Overviews and Summaries

The CTD overviews and summaries are the same as that described in [section 15.2](#) in Chapter C *New Drug Application Submission*.

21.3 Quality Documents

The full set of quality documents (i.e. Module 3 of ICH CTD or Part II of ACTD) should be submitted.

Data submitted should include extensive drug substance and drug product characterisation and quality comparability data between the biosimilar product and the Singapore reference biological product. The comparability exercise should encompass both the drug substance and the drug product and should also take the following into consideration:

- the complexity of the molecular structure;

- the types of changes introduced in the manufacturing process during development; and
- the impact on quality, safety and efficacy.

21.4 Non-clinical and Clinical Documents

Non-clinical and clinical data generated with the biosimilar product are required.

The amount of non-clinical and clinical data required will depend on:

- the product or class of products;
- the extent of characterisation which is possible to undertake when using state-of-the-art analytical methods;
- observed or potential differences between the biosimilar product and the reference biological product; and
- the clinical experience with the product class.

A case-by-case approach is needed for each class of products.

Submission of RMPs in support of all biosimilar applications is mandatory. Guidance on risk management plan submission requirements can be found in Appendix 16 *Guideline on the Submission of Risk Management Plan Documents*.

CHAPTER F POST-APPROVAL PROCESS

Throughout the life cycle of a therapeutic product, changes to a product's efficacy, quality and/or safety are likely to occur. HSA must be notified of any changes to a product's safety, efficacy or quality through an application process – i.e. the variation application.

22 APPLICATION TYPES

Figure 5 is a schematic diagram illustrating the various types of variation applications:

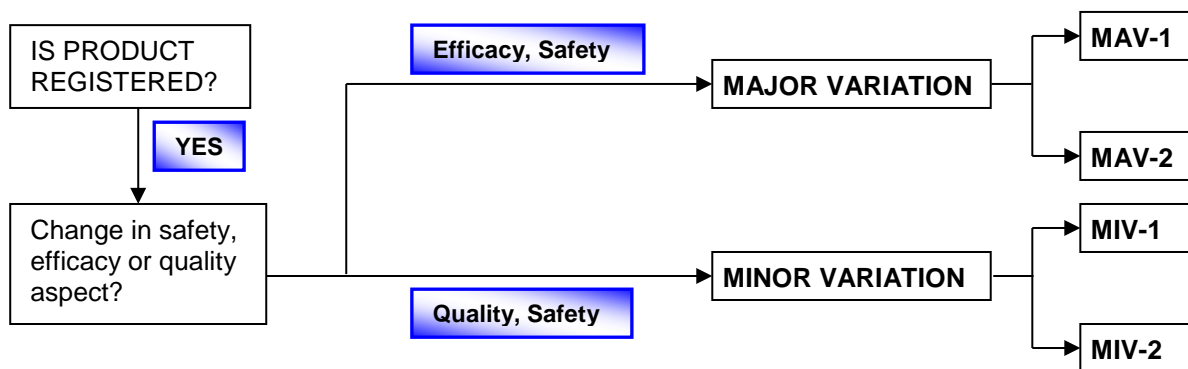


Figure 5 Schematic diagram of variation application routes.

There are two types of variation applications – major variation applications (MAV) and minor variation applications (MIV). The different variations and application types are described as follows:

MAV Major Variation application for an existing registered product.

MAV-1: Any variation to the approved indication(s), dosing regimen(s), patient group(s), and/or inclusion of clinical information extending the usage of the product (e.g. clinical trial information related to an unapproved indication, dosing regimen and/or patient population; recommendations for concomitant administration of vaccines; additional bacterial strains with clinical (*in vivo*) data to expand the indication(s) for antimicrobial products; additional viral serotypes/genotypes to expand the indication(s) for antiviral products, etc.).

MAV-2: A change in the current approved forensic classification, also known as reclassification.

MIV Minor Variation application for an existing registered product

MIV-1: A minor variation to the quality aspects, i.e. chemistry, manufacturing controls and/or product labelling.

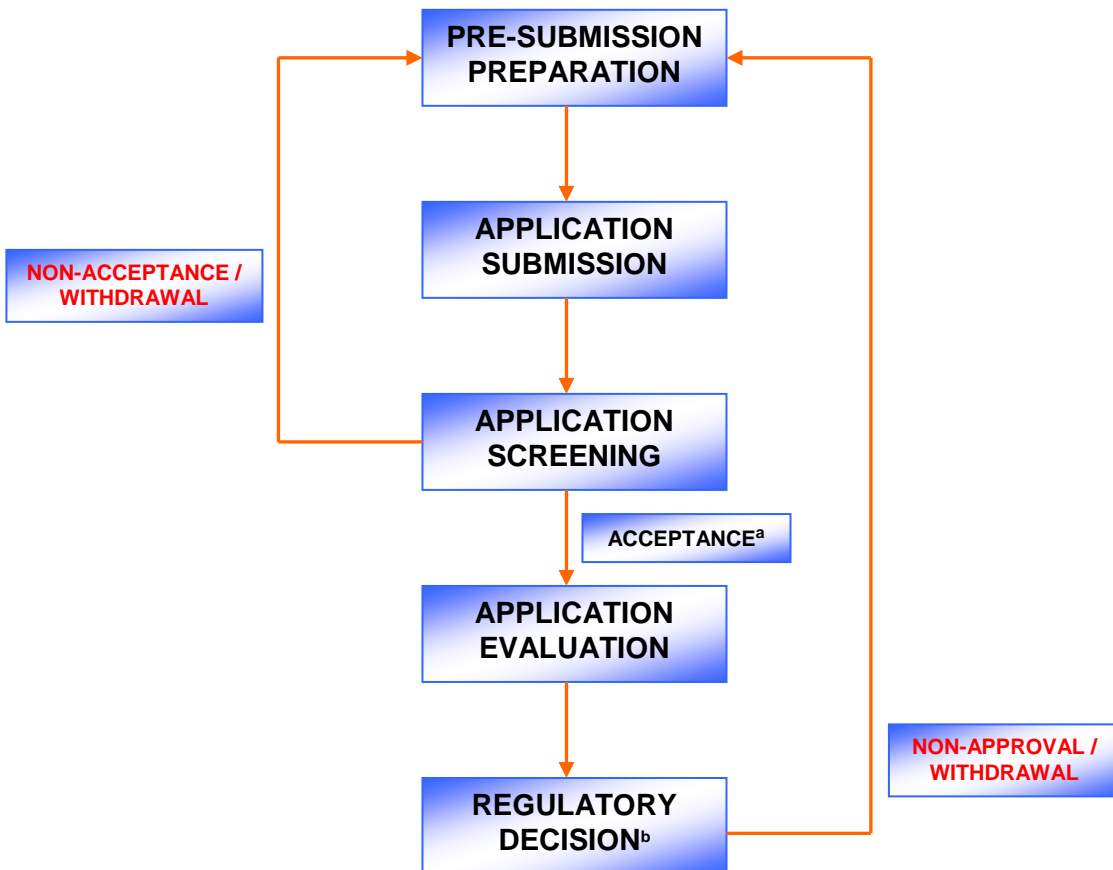
MIV-2: A minor variation or an administrative change.

HSA may re-categorise the application type if appropriate. Applicants are to note that, in PRISM, the re-categorisation of an application (e.g. MIV to MAV-1, MIV-2 to MIV-1, or *vice versa*) may require the withdrawal of the original application. Applicants will be notified if they are required to resubmit the application according to the correct category.

All applications require HSA's approval before the change(s) can be implemented, with the exception of MIV-2 applications, where the change(s) can be implemented if there is no objection from HSA within the notification timeline (refer to Appendix 5 *Target Processing Timeline* for notification timeline).

23 VARIATION APPLICATION PROCESS

The steps to follow when submitting an MAV or MIV are similar to those for submitting an NDA or GDA, as seen in Figure 6:



^a An acceptance notice will not be sent for MIV-2 applications.

^b A regulatory decision letter will not be sent for MIV-2 applications.

Figure 6 Schematic Diagram of the Variation Application Process.

However, each variation application has distinct differences and the applicant should be familiar with the variation application process in order to facilitate the process.

For information on the variation application processing time, refer to Appendix 5 *Target Processing Timeline* of this guidance document.

23.1 Pre-Submission Preparation

Applicants are advised to ensure that all the requirements for the variation application are met before submitting the application.

Applicants are encouraged to contact HSA prior to the submission of a variation application if there are questions regarding the application. There are two methods to contact HSA:

- (a) Pre-submission Enquiry via the [online feedback form](#) on the HSA website; and
- (b) Pre-submission Consultation/ Notification.

Applicants are to note that all advice given by HSA will be based on knowledge that is current at the time of the consultation. Such advice is not binding and does not have a direct bearing on the eventual outcome of the application concerned.

23.1.1 Pre-Submission Enquiry

The applicant may submit a Pre-Submission Enquiry via the [online feedback form](#) on the HSA website if any clarification on submitting an MAV application is needed prior to submission.

For issues relating to MIV submissions, the applicant should submit a completed MIV Filing and Submission Enquiry Form (Appendix 12) via the [online feedback form](#) on the HSA website. Upon the receipt of an MIV Enquiry Form, an officer will look into the enquiry and respond to the named applicant via email with an Enquiry Reference Number. If the MIV is submitted, then a copy of the Enquiry Form, with the Enquiry Reference Number, should be included in the submission.

23.1.2 Pre-Submission Meeting/ Notification

An applicant may request for a pre-submission meeting if a face-to-face consultation with HSA is necessary to address specific submission issues. The request should be made in writing, stating the purpose, agenda and proposed date and time for the meeting, via the [online feedback form](#) on the HSA website.

The meeting request should be made at least 3 weeks prior to the meeting date, and relevant meeting documents (e.g. presentation slides, briefing documents, etc.) should be provided at least 1 week before the meeting.

A pre-submission meeting is not compulsory for an application filed via the full evaluation route (see [section 24.1 Evaluation Routes](#) for more information on MAV-1 evaluation routes). Nonetheless, the applicant is required to notify HSA at least two months prior to the intended submission date. The notification can be sent via the [online feedback form](#) on the HSA website, and should include information on the product name (if available), active ingredient(s), summaries of the clinical data (e.g. Overviews), planned submissions in other countries, and planned date of submission to HSA.

23.2 Application Submission

The submission of an application comprises two key steps – (i) online submission of the application form via [PRISM](#) and (ii) submission of the technical dossier.

23.2.1 PRISM Application Form

The procedure for submitting the variation application through PRISM is similar to that for a NDA or GDA, although some fields in the PRISM application form are disabled for variation applications.

Applicants should refer to Appendix 17 *Guideline on PRISM Submission* for further details.

23.2.2 Variation Application Dossier

The technical dossier accompanying the application should be submitted within 2 working days of the PRISM application submission to prevent delays in the processing of the application. **The date of receipt of the actual technical dossier by HSA will be taken as the submission date where the processing time starts.**

The dossier submitted for variation applications should be in the **same CTD format** as that used for the original new product application.

Application checklists for both ICH CTD and ACTD dossiers are provided in Appendix 2B and 3B, respectively, to guide applicants on the submission requirements and to ensure completeness of the dossier. **Each MAV application must be accompanied by a checklist duly completed by the applicant and attached in PRISM.**

23.2.2.1 Submission Requirements

The complete application dossier – i.e. Modules 1 to 5 of the ICH CTD or Parts I to IV of the ACTD – must be submitted in an electronic format.

All documents required under Module 1/Part I must be submitted in softcopy in PRISM. Colour scanned copy of the original documents should be submitted and original hardcopy of documents are not required. However, HSA reserves the rights to request for the submission of the original or certified true copy of the submitted document if there is any doubt that the submitted scanned document is not an accurate reflection of the original document.

Please refer to [section 23.2.2.3](#) for more information on certifying non-original documents if the original documents cannot be provided.

For Modules 2 to 5/Parts II to IV, applicants can opt to attach the documents either in full into PRISM section 7 (Supporting Attachments) or submit the softcopies (e.g. PDF format) in a CD/DVD.

For submission requirements for MIV applications, please refer to Appendix 13 and Appendix 14 for registered chemical products and registered biological products, respectively.

Submitting a CD or DVD

When submitting a CD/DVD, applicants are encouraged to organise the dossier (i.e. folders and subfolders) according to the CTD format and to include bookmarks in all documents to facilitate retrieval of documents.

Files containing the below scripts will not be accepted due to cybersecurity reasons:

S/N	Script Type	Extension
1	VB Script	*.vbs, *.vbe, *.vb
2	VBA	*.vba
3	JS Script	*.js, *.jse
4	Windows Script File	*.wsf, *.ws
5	Windows Script Component	*.wsc, *.wsh
6	Powershell	*.ps1, *.ps1xml, *.ps2, *.ps2xml, *.psc1, *.psc2
7	Monad (legacy Powershell)	*.msh, *.msh1, *.msh2, *.mshxml, *.msh1xml, *.msh2xml
8	Windows Shell	*.com
9	Batch	*.bat, *.cmd
10	Python	*.py, *.pyo, *.pyc, *.pyw, *.pys
11	Perl	*.pl, *.pls, *.p
12	Shortcut	*.lnk

The CD/DVD should be properly labelled with the following information:

- PRISM application number;
- PRISM submission date;
- Product name;
- Application type; and
- Contents of the CD/DVD (e.g. Module 2 and 5).

Applicants must ensure the access to the content of CD/DVD. For protected files, password(s) must be provided as appropriate.

Upon acceptance of the application for evaluation, applicants will be notified if additional copies of clinical documents (in CD/DVD) will be required.

23.2.2.2 Language and Translation

All documents submitted in support of an application to HSA must be in English. For documents in original language which is not English, a certified translation or a verified translation may be acceptable.

<u>Translation type</u>	<u>Type of Documents</u>	<u>Requirements</u>
Certified Translation	<ul style="list-style-type: none"> ▪ Official certificates issued by the drug regulatory agency of a country ▪ Proof of approval issued by the drug regulatory agency of a country 	<p>Notarisation & Authentication</p> <p><u>(a) Notarisation</u></p> <ul style="list-style-type: none"> ▪ These documents must be notarised by a notary public in country where document is issued. ▪ Details of particulars to be included by notary: <ul style="list-style-type: none"> (i) The name of the notary; (ii) A statement that the notary is duly admitted to practice in the place of issue of the certificate; (iii) The names of the signatories and the capacity in which they have executed the document, whether on their own behalf or in an official or representative capacity; (iv) A statement authenticating the signatures of the parties and, where appropriate, indicating that evidence has been produced to the notary proving the capacity in which they have executed the document; (v) The place and date of issue of the notarial certificate; and (vi) The signature and seal of the notary. <p><u>(b) Authentication</u></p> <ul style="list-style-type: none"> ▪ These documents must be authenticated (i.e. the origin of the document is attested to) by one of the following government bodies:-

		<p>(i) The Ministry of Foreign Affairs of the country in which the document was issued; or</p> <p>(ii) The Singapore Embassy/Consulate in the country where the document was issued.</p> <p>Applicants are advised to consult the Singapore Embassy/Consulate in the country where the document originated regarding the local requirements for document legalisation, as these may deviate from the process as outlined in the preceding paragraph.</p>
Verified Translation	<ul style="list-style-type: none"> ▪ Technical documents (e.g. package insert, submission dataset) 	<p>Verification Document</p> <ul style="list-style-type: none"> ▪ A verification document must be provided by the translator of the document into the English language. ▪ The verification document must state that the translation into English is accurate. ▪ Details of particulars to be included in verification document: <ul style="list-style-type: none"> (i) the name of translator; (ii) a statement that he/she is well versed in English and the relevant foreign language; and (iii) a reference to the document being translated. <p>Refer to the sample verification document for translator enclosed in Appendix 4.</p>

23.2.2.3 Certifying non-original documents

If the softcopy official document (e.g. CPP, GMP certificate, etc.) submitted to HSA in PRISM is not a scan of the original document, the document must be certified

prior to submission. A certified true copy certifies that the photocopy presented is a true and accurate copy of the original document. Acceptable certification of documents to support drug product applications to HSA can be done by the Company Director or Company Secretary as registered with ACRA or above, or by an independent authority such as a lawyer, notary public, Commissioner for Oaths/Declarations/Affidavits, Justice of Peace, the original issuer of the document or Embassy/Consulate. A notarised and authenticated copy is the same as a certified true copy.

A certified true copy of approval letters requires certification by the drug regulatory agency that issued the approval letter, notary public or Singapore Embassy/Consulate in the country where the approval letter was issued. Certification of approval letters is not required in the event the approval letter is available on the drug regulatory agency's website. In this instance, applicants should provide the internet address (URL) for validation by HSA.

23.3 Application Screening

The screening process for a variation application is similar to that for an application for a new therapeutic product.

The application will be screened to ensure the correctness of the application type and the completeness of the dossier. **The date of receipt of the application dossier (i.e. the technical dossier [e.g. in a CD/DVD] including the application checklist) will be taken as the submission date and the start of the screening timeline.**

During screening, if an application is identified to be more appropriately submitted under a different application type, the applicant will be informed of this change and the necessary actions to effect this change via an Input Request. More information on the change in application type is described in [section 23.6.2.1 *Changes to Application Types and Re-routing of Evaluation During Screening*](#).

An MAV application submitted without the clinical dossier or an application submitted via the verification route without assessment reports will not be screened,

as screening cannot proceed without the dossier. A non-acceptance letter will be issued, following which the PRISM application will be withdrawn by HSA and the dossier will be returned to the applicant.

Applicants are also advised to ensure that the dossier is compiled according to the required format. Failure to adhere to the required CTD format will lead to the non-acceptance of the dossier without screening.

If the dossier submitted is considered to be otherwise incomplete, a screening query letter stating the deficiencies will be issued via PRISM (Input Request) to the applicant. The stop-clock starts when an Input Request is sent and ends upon receipt of a complete and satisfactory response to the query. For MAV applications, the total number of Input Requests sent during screening is capped at two. Applicants will be given 20 working days to respond to each Input Request, starting from the date the Input Request is sent.

The application will only be accepted when all deficiencies have been adequately addressed and HSA is satisfied that the dossier is complete for evaluation. An acceptance notice will then be issued via email (only applicable for MAV and MIV-1 applications). The date of acceptance of the application will be taken as the start of the evaluation timeline.

If the applicant fails to address the deficiencies raised during screening, the dossier is considered incomplete for evaluation. A non-acceptance letter will be issued, following which the PRISM application will be withdrawn by HSA and the dossier will be returned to the applicant. If the application is subsequently re-submitted, it will be processed as a new application.

NOTE: The screening process only checks for completeness of the application dossier for evaluation. The acceptance of the dossier for evaluation does not denote the adequacy of the data for regulatory approval.

23.4 Application Evaluation and Regulatory Decision

The evaluation process for a variation application is similar to that for an application for a new therapeutic product.

Once the application is accepted, the evaluation stage begins. A query letter may be issued to the applicant if clarification or additional information is required.

The stop-clock starts whenever HSA issues a query letter and ends upon the receipt of a complete and satisfactory response from the applicant.

In situations where the applicant is unable to provide a complete response within the specified timeframe, the applicant should notify HSA as soon as possible after receiving HSA's queries. The application will be considered withdrawn if the applicant fails to observe the specified response deadline.

Applicants are reminded that the submission of additional supporting data not requested by HSA following the acceptance of the application will not be considered, unless prior arrangement with HSA is made for the submission concerned. During the evaluation process, HSA may assess that the application is more suitably evaluated via an alternative route, in which case the application will be re-routed to the appropriate route. Any re-routing of the application will be discussed with the applicant.

HSA may engage external evaluators, experts and advisory committees in the evaluation process, when necessary. These experts include scientists and clinicians from both local and overseas institutions. All external evaluators and experts are bound by agreement to protect the information made available to them. The identity of the external evaluators is kept confidential.

For MAV-1 applications (full and abridged evaluation routes), applicants can check on the progress of the evaluation and may view the evaluation stage via [Track@PRISM](#). Table 10 describes the stages of the evaluation process for MAV-1 applications.

Table 10 Variation Applications Applicable for Notification of Stages During Evaluation

Stages of Notification to Applicant		1 st Stage	2 nd Stage	3 rd Stage	4 th Stage
Application Type	Evaluation Route	Evaluation Status			
		Acceptance for Evaluation	Active Evaluation in Progress	Evaluation at Midway	Completed Evaluation
MAV-1	Full or Abridged	<p>Application is accepted for evaluation</p> <p>This marks the start of the evaluation timeline</p>	<p>When active evaluation is in progress for the application</p>	<p>Application is approximately midway through the evaluation (provided that there were no prior stop-clocks which may affect the evaluation progress)</p> <p>Applicants could expect to receive the first set of queries from HSA during this stage</p>	<p>Evaluation is completed for the application</p> <p>Application is now undergoing the regulatory decision phase, after which a regulatory decision letter* would be issued.</p> <p>Applicants could still expect further queries from HSA during this stage</p>

* The issuance of a regulatory decision letter would mark the end of the evaluation timeline for a product application.

The following screenshots illustrate the change in stages of a pending application:

PZ0951 TRACK@PRISM**Important Notes:**

For HSA CRIS registered companies, user has to be authorised with the appropriate access rights via CRIS management module to access the required eservices.

General Search

Enter Transaction No or Application/Submission No for fast and exact matched look-up

Application/Submission Type *

Licence/Permit/Certificate/Listing/Notification/Registration Type *

Enquiry Type *

Transaction No.

Application/Submission No.

Licence/Permit/Certificate/Listing/Notification/Registration No.

Product Name.

Submission Date (dd/mm/yyyy) To

Last Update Date (dd/mm/yyyy) To

Choose these options from the drop-down lists.

Enter PRISM application to view stage of evaluation.

[Please click here to extend your draft](#)

1 Matching Record(s) Page 1 Of 1 [First] | [Previous] | [Next] | [Last]

New Application/Submission for Therapeutic Products - Product Registration (Pending Approval)								
S/No	Application No	Transaction No	Product Name	Application/Submission Status	Submission Date	Last Updated Date	Copy Application	Withdraw Application
1	1600464U	T1600883K	Product ABC	Active Evaluation	05/04/2016	08/04/2016	Copy to draft	Withdraw

The evaluation stage is seen here.

Applicants are also notified via system-generated emails whenever an evaluation stage change occurs.

The regulatory decision process for a variation application is also similar to that for an application for a new therapeutic product. However, a regulatory decision letter will not be issued for MIV-2 applications as these are notifiable changes.

Upon approval/notification of a variation application, the product registration information in PRISM will be updated to reflect the changes (if applicable). Registrants may refer to [Enquire@PRISM](#) to view the latest product registration information of their products.

Registration conditions and post-approval commitments may also be applicable to variation applications. Registrants must take note of the updated registration conditions and the post-approval commitments specified in the registration. The registration conditions can be viewed at [Enquire@PRISM](#).

23.5 Target Processing Timelines

Please refer to Appendix 5 for information on target processing timelines for the different application types and evaluation routes.

23.6 Fees

As the fees may be subject to revision from time to time, applicants are advised to visit the [HSA website](#) for updated information on fees.

Payment can be made via GIRO or other electronic payment modes such as eNets or eCredit card.

NOTE: Applicants are strongly encouraged to apply for a GIRO account ([click here for GIRO application form](#)) with HSA to facilitate payments for future submissions and subsequent payment for retention fee for the registered products.

23.6.1 Screening Fee

The screening fee is only applicable for MAV-1 applications and is payable at the time of online submission via PRISM. The screening fee is non-refundable once the application is submitted via PRISM.

For payment via GIRO, the screening fee will be debited upon the successful submission of an online application.

For payment via other electronic payment modes, the screening fee must be paid before the application is considered successfully submitted online.

A screening fee is not applicable for other types of variation applications.

23.6.2 Evaluation Fee

There are two different evaluation fees for MAV-1 applications:

- (a) Evaluation fees for a single-strength product or the first product in a series of products of different strengths; and
- (b) Evaluation fees for each subsequent product in a series of products of different strengths.

An evaluation fee for a MAV-1 application is payable upon the acceptance of the dossier for evaluation and is non-refundable once the application is accepted.

An evaluation fee for a MIV-1 application is payable upon the submission of the application in PRISM and is non-refundable.

For payments via GIRO, the evaluation fee will be debited upon the acceptance of the application.

For payments via other electronic payment modes, the evaluation fee will be collected together with the screening fee. In the event that the application is not accepted for evaluation, the fee collected will be refunded to the applicant.

Applicants may opt for the progressive payment scheme. This is an opt-in scheme eligible for applicants who make payment via GIRO and is only applicable to the application types listed in Table 11:

Table 2 Variation Applications Applicable for Progressive Payment Scheme

Percentage of Evaluation Fee Payable at Each Stage					
Application Type	Evaluation Route	Evaluation Status			
		Acceptance for Evaluation	Active Evaluation in Progress	Evaluation at Midway	Completed Evaluation
MAV-1	Full or Abridged	30%	40%	20%	10%

Once the application is submitted, the selected payment scheme (full or progressive) cannot be amended. Applicants who wish to change their selected payment scheme will have to withdraw and re-submit the application(s); and any upfront payment made (e.g. screening fee) are non-refundable.

For applications under the progressive payment scheme, in the event that the application is withdrawn during the evaluation stage, any fees that had been charged, but not debited from the GIRO account would remain payable. Any paid fee is non-refundable.

23.6.2.1 Changes to Application Types and Re-routing of Evaluation During Screening

If an application type or evaluation route is incorrectly selected, applicants will be informed via an Input Request. Such changes may result in a different **evaluation fee** upon acceptance of the application.

In the situation where the applicant decides not to pursue the application due to the said changes, the screening fee is not refundable.

For applications which require withdrawal and resubmission, the screening fee is not refundable. Applicants may wish to seek clarification on appropriate application type or evaluation route via the [online feedback form](#) on the HSA website prior to the submission.

23.6.2.2 Change of Application between Different Application Types

This refers to a change in the application type between MAV-1, MAV-2, MIV-1 or MIV-2.

The applicant will be required to withdraw and resubmit the application if the applicant intends to pursue the application.

23.6.2.3 Change of Evaluation Route

This refers to a change in evaluation route (e.g. Full to Abridged, Verification to Abridged, Abridged to Verification, etc.).

The applicant will be required to withdraw and resubmit the application if the applicant intends to pursue the application.

CHAPTER G MAJOR VARIATION (MAV) APPLICATION SUBMISSION

This chapter applies to major variation applications for currently registered products.

24 MAV-1 APPLICATIONS

An MAV-1 application applies to variations to any of the following:

- (a) approved indication(s);
- (b) approved dosing regimen(s);
- (c) approved patient group(s); and/or
- (d) inclusion of clinical information extending the usage of the product – for example, clinical trial information related to an unapproved indication, dosing regimen and/or patient population; recommendation for concomitant administration of vaccines; additional bacterial strains with clinical (*in vivo*) data to expand the indication(s) for antimicrobial products; additional viral serotypes/genotypes to expand the indication(s) for antiviral products, etc.

For each product registration, applicants may submit up to a maximum of three concurrent MAV-1 applications at any one time.

24.1 Evaluation Routes

There are three evaluation routes for an MAV-1 – full, abridged and verification evaluation routes. The eligibility criteria and documentary requirements are different for each evaluation route.

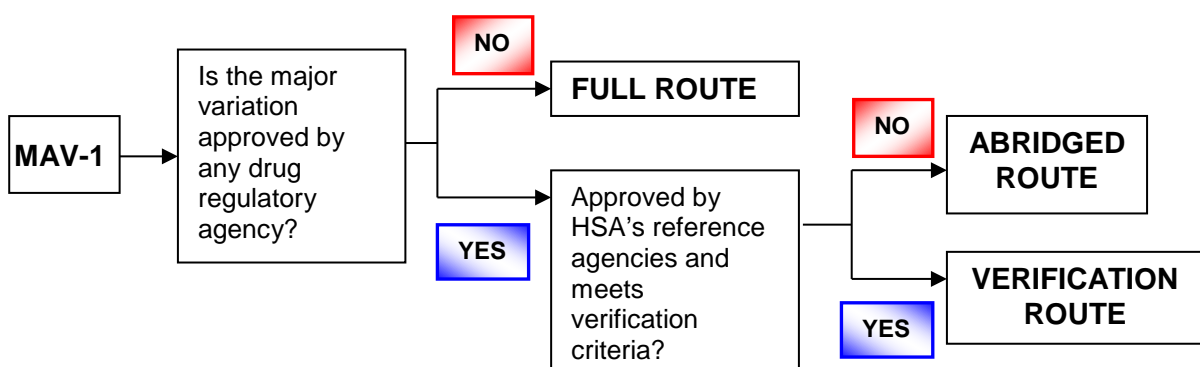


Figure 7 Schematic Diagram of Evaluation Routes for MAV-1s

24.1.1 Full Evaluation Route

Full evaluation will apply to a major variation that has not been approved by any drug regulatory agency at the time of submission.

For a submission under the full evaluation route, the applicant is required to notify HSA via the [online feedback form](#) on the HSA website at least two months prior to the intended submission date of the application dossier. The notification should include information on the product name (if available), active ingredient(s), summaries of the quality, non-clinical and clinical data (e.g. Overviews), planned submissions in other countries, and the planned date of submission to HSA.

24.1.2 Abridged Evaluation Route

Abridged evaluation applies to a major variation that has been evaluated and approved by at least one drug regulatory agency. The proposed variation – i.e. the proposed indication(s), dosing regimen(s), patient group(s) and/or clinical information – should be the same as that approved by the regulatory agency that issued the proof of approval.

24.1.3 Verification Evaluation Route

Similar to an NDA, at least two of HSA's reference drug regulatory agencies must have evaluated and approved the major variation. However, approval by these reference regulatory agencies does not oblige HSA to approve the application.

One of the reference drug regulatory agencies must be declared as the primary reference agency. The chosen primary reference agency is defined as the reference drug regulatory agency from which the qualifying supporting documents (as outlined in this guidance) will be submitted and which approved the strictest indication(s), dosing regimen(s), patient groups(s) and/or direction(s) for use among the two reference drug regulatory agencies which approved the variation.

Additional eligibility criteria for the verification route include:

- The application must be submitted within three years from the date of approval by the chosen primary reference agency;
- The product does not need a more stringent assessment as a result of differences in local disease patterns and/or medical practices (e.g. some anti-infectives); and
- The product and its intended use – i.e. indication(s), dosing regimen(s) and patient group(s) – have not been rejected, withdrawn, approved via appeal process or pending deferral by a drug regulatory agency for safety and/or efficacy reasons.

The proposed indication(s), dosing regimen(s), patient group(s) and/or direction(s) for use should be the most stringent amongst those approved by the reference regulatory agencies.

For a product with a proposed indication that has been designated as an Orphan Drug by at least one reference drug regulatory agency or a product that has been approved by at least one reference drug regulatory agency via an accelerated/fast-track approval, approval under exceptional circumstances or equivalent approval process, the applicant should consult HSA on the eligibility of such a product through the verification route prior to its submission. Please refer to [section 23.1 Pre-submission Preparation](#) for the available channels to consult HSA.

24.2 Documentary Requirements

Table 12 outlines the CTD Modules/Parts required for MAV-1s submitted under each evaluation route:

Table 3 Dossier Submission Requirements for MAV-1s

	Location in		Module/Part required for		
	ICH CTD	ACTD	Full MAV-1	Abridged MAV-1	Verification MAV-1
Administrative Documents and Product Information	Module 1	Part I	Yes	Yes	Yes
Common Technical Document Overview and Summaries	Module 2	<i>Incorporated into Parts II, III and IV</i>	Yes	Yes	Yes
Quality documents	Module 3	Part II	No	No	No
Non-clinical documents	Module 4	Part III	No [§]	No [#]	No [#]
Clinical documents	Module 5	Part IV	Yes	Study report(s) of pivotal studies and synopses of all studies (phase I-IV) relevant to requested indication, dosing and/or patient group	Study report(s) of pivotal studies and synopses of all studies (phase I-IV) relevant to requested indication, dosing and/or patient group

§ If the proposed MAV-1 is related to non-clinical data, non-clinical summary and non-clinical overview as well as relevant study reports is required.

Non-clinical overview only, if applicable.

24.2.1 Administrative Documents

The three evaluation routes for an MAV-1 share the same documentary requirements for CTD Module 1/Part I. The documents required are:

(a) Section 1.1 – Comprehensive Table of Contents;

NOTE: Applicants must complete the relevant checklists found in Appendix 2B or Appendix 3B and attach the completed checklist under PRISM section 1.2

(b) Section 1.2 – Introduction – including the *Table of Amendment Details* of PRISM section 0.5;

(c) Section 1.3 – PRISM application form;

(d) Section 1.4 – Labelling, Package Insert and Patient Information Leaflet – both the proposed and currently approved Singapore product labels and PI/PIL are required. For the proposed labelling/PI/PIL, a pristine and an annotated version (which highlights the changes made to the currently approved labelling) are required. Annotations should be made on the proposed labelling materials based on the actual text to be added, and on current approved labelling materials. Current approved text proposed for deletion should be struck through, whereas newly added and proposed text should be underlined or highlighted. Current approved text that is not intended to be deleted should not be annotated. However, the translocation of current approved text from one section to another can be allowed in its entirety.

(e) Section 1.5 – Approved SPC/PI/PIL from the drug regulatory agency that issued the proof of approval and from each of HSA's reference drug regulatory agencies (where applicable);

(f) Section 1.6 – Assessment Report from Reference Agencies – only for verification route (see [section 24.2.5.3 Verification Evaluation Route](#));

(g) Sections 1.8, 1.9 – Proof of Approval – for an MAV-1, the official approval letter(s) must contain information on the requested Singapore variation. For the

verification evaluation route, the approval letters issued by at least two reference drug regulatory agencies, including the chosen primary reference agency, should be submitted;

(h) Section 1.13 – Declaration on rejection, withdrawal and deferral; and

(i) Section 1.15 – Registration Status in Other Countries.

24.2.2 CTD Overviews and Summaries

The following documents are to be submitted:

- a non-clinical overview, if applicable; and
- a clinical overview and summaries of clinical efficacy and clinical safety.

24.2.3 Quality Documents

Quality documents (Module 3/Part II) are not required for MAV-1 applications.

24.2.4 Non-clinical and Clinical Documents

Each evaluation route will have different non-clinical and clinical documentary requirements. Refer to [section 24.2.5 Specific Documentary Requirements for Each Evaluation Route](#) below for more information.

For MAV applications, HSA may request for RMPs to be submitted on a case-by-case basis following the evaluation of the safety concerns described in the product application, where necessary. For such instances, please refer to the guidance on RMP submission requirements found in Appendix 16 *Guideline on the Submission of Risk Management Plan Documents*.

If the MAV-1 is for a non-prescription medicine and is submitted via the abridged evaluation route, the applicant may submit a written request for a waiver of clinical data submission. Eligibility for a waiver is subject to the criteria defined in Appendix 6 *Guideline on Submission for Non-Prescription Therapeutic Products*. However, HSA may request for the complete clinical data set if it is deemed appropriate.

24.2.5 Specific Documentary Requirements for Each Evaluation Route

24.2.5.1 *Full Evaluation Route*

The technical documents required include:

- complete non-clinical documents, if applicable; and
- complete clinical documents; i.e. all study reports from phase I to phase III, including tables and appendices.

24.2.5.2 *Abridged Evaluation Route*

The technical documents required include:

- a non-clinical overview, if applicable; and
- a clinical overview, summaries of clinical efficacy and clinical safety, synopses of relevant studies, a tabular listing of the clinical development programme and study reports of the pivotal studies (the tables and appendices to the pivotal study reports may be submitted upon request by HSA).

24.2.5.3 *Verification Evaluation Route*

The complete assessment report and other relevant supporting documents from the **chosen** primary reference agency must be submitted, as tabulated below. The assessment reports from the primary reference agency must be unredacted or unedited, and should include details of imposed licensing conditions, final product labelling, clinical reviews, and other information in relation to the product's approval. Reports obtained from the public domain are deemed unacceptable.

Applications submitted to HSA without the unredacted/ unedited reports from the primary reference agency will not qualify for the verification evaluation route. The applicant will be required to withdraw and resubmit the application via the abridged route if the applicant intends to pursue the application.

Primary reference agency	Documentary requirements
Health Canada	<ul style="list-style-type: none"> • Complete Clinical assessment reports, including assessment on the Question & Answer documents between the Sponsor & Agency and all annexes
US FDA	<ul style="list-style-type: none"> • Complete Clinical assessment reports, including assessment on the Question & Answer documents between the Sponsor & Agency and all annexes* <p><i>* Companies who face difficulties in obtaining the unredacted reports can submit the “FDA Sponsor’s Authorization” (signed by the product’s Sponsor in the US) to HSA prior to the submission of the registration application, and HSA will help to facilitate the retrieval of the reports. The application should only be made after HSA receives the assessment reports from FDA. The unredacted assessment reports are pre-requisites at the point of making the application and the submission of the “FDA Sponsor’s Authorization” alone does not qualify the application for verification.</i></p>
UK MHRA	<ul style="list-style-type: none"> • Complete Clinical assessment reports, including assessment on the Question & Answer documents between the Sponsor & Agency and all annexes† <p><i>† All assessment reports (interim and final) (e.g. Day 70, Day 120 Day 200, etc., according to the respective EU procedure), all question and answer documents, and all other relevant documents (e.g. comments from CMS for MRP/DCP) should be submitted in accordance with the respective EU procedure:</i></p> <ul style="list-style-type: none"> - National Procedure - Mutual Recognition Procedure [where UK MHRA acted as the RMS] - Decentralised Procedure [where UK MHRA acted as the RMS]

Primary reference agency	Documentary requirements
EMA	<ul style="list-style-type: none"> • Complete Clinical assessment reports, including assessment on the Question & Answer documents between the Sponsor & Agency and all annexes[‡] <p><i>‡ All assessment reports (interim and final) (e.g. Day 80, Day 120, Day 150, Day 180, etc.), all question and answer documents, and all other relevant documents should be submitted in accordance with the EU Centralised Procedure.</i></p> <p><i>Companies who face difficulties in obtaining the unredacted reports can submit the EMA form for “Applicant’s Consent to Share Assessment and Inspection Documents with Non-European Union (EU) Regulatory Authorities” (signed by the product’s MAH in the EU) to HSA prior to the submission of the registration application, and HSA will help to facilitate the retrieval of the reports. The application should only be made after HSA receives the assessment reports from EMA. The unredacted assessment reports are pre-requisites at the point of making the application and the submission of the “Applicant’s Consent to Share Assessment and Inspection Documents with Non-European Union (EU) Regulatory Authorities” alone does not qualify the application for verification.</i></p>
TGA	<ul style="list-style-type: none"> • Complete Clinical assessment reports, including assessment on the Question & Answer documents between the Sponsor & Agency and all annexes • Delegate’s overview • Pre-ACPM response • ACPM minutes

The technical documents required include:

- a non-clinical overview, if applicable; and
- a clinical overview, summaries of clinical efficacy and clinical safety, synopses of relevant studies, a tabular listing of the clinical development programme and

study reports of the pivotal studies (the tables and appendices to the pivotal study reports may be submitted upon request by HSA).

All of the data submitted to HSA must be the same as the data package submitted to the reference drug regulatory agencies. Differences between the dossier submitted to HSA and data reviewed by the reference drug regulatory agencies will not only delay the processing of the application, but may also lead to the re-routing of the dossier to the abridged evaluation route if significant undisclosed differences are discovered.

25 MAV-2 APPLICATIONS

An MAV-2 application applies to variations involving a change in forensic classification of a registered product, otherwise known as “reclassification”. Examples of reclassification include from POM to P or from P to GSL. Applicants are advised to refer to [section 1.2 Forensic classification](#) for more information.

If an MAV-2 application is riding on a previous reclassification of an analogous product, then the applicant may submit a ‘me-too’ reclassification (see [section 25.2.1 'Me-too' Reclassification](#)). Reclassification may also be undertaken when experience gained shows that there is a need to supervise the use of a product – i.e. from GSL to P or POM.

More information on reclassified medicines may be found on the [HSA website](#).

25.1 Evaluation Routes

Only the abridged evaluation route applies for MAV-2 applications.

25.2 Eligibility Criteria

A change of forensic classification of a POM or P drug product to a less stringent classification may be considered if the following criteria are met:

- (a) The use of the product has been sufficiently extensive;

- (b) The product has been marketed for a period of time sufficient to establish a post-marketing adverse event profile;
- (c) The product's safety profile gives no cause for concern during the marketing period; and
- (d) The product is presented in an appropriate pack size with consumer-friendly labelling (PIL/outer carton).

Applicants who wish to submit a request for the reclassification of a therapeutic product should provide justifications based on the following information:

- (a) The forensic classification and approved indication(s) and dosing regimen(s) of the product in the UK, US, Canada and Australia, where applicable
- (b) The period of product registration in Singapore, UK, US, Canada and Australia, where applicable, with specific information on its forensic classification (i.e. POM, P and/or GSL) and duration of sale in that classification;
- (c) The period of actual product sale in Singapore;
- (d) The rationale for requesting a change in the forensic classification;
- (e) Patient exposure to the product and its safety profile based on worldwide spontaneous adverse drug reaction reports, data from post-marketing surveillance studies, clinical trials, published literature and locally reported adverse drug reactions; and
- (f) Potential problems and hazards arising from the inappropriate use of the product.

25.2.1 'Me-too' Reclassification

A 'me-too' reclassification will be considered if the forensic classification of the product is to be aligned with that of a similar product with the same active ingredient and intended use.

25.3 **Documentary Requirements**

One set of documents, as outlined in the checklists in Appendix 2B or Appendix 3B, should be submitted in softcopy.

The documentary requirements for an MAV-2 submission include:

- (i) Section 1.1 – Comprehensive Table of Contents;

NOTE: Applicants must complete and submit the relevant checklists found in Appendix 2B or Appendix 3B under PRISM section 1.2

- (ii) Section 1.2 – Introduction – including the justification for reclassification, as listed above, and the *Table of Amendment Details* of PRISM section 0.5;
- (iii) Section 1.3 – PRISM Application Form;
- (iv) Section 1.4 – Product Labels – the proposed product labels/PIL should also be submitted, if applicable;
- (v) Section 1.5 – Approved SPC/PI/PIL;
- (vi) Section 1.8 – Proof of Approval – proof of the approved indication(s) and dosing regimen(s) for the reclassified product in the UK, US, Canada and/or Australia;
- (vii) Section 1.15 – Registration Status in Other Countries; and,
- (viii) Module 2/Part IV – Summary of Clinical Safety – the summary should include the following:
- (i) The forensic classification of the product in the UK, US, Canada and Australia, with specific information on its forensic classification and duration of sale in that classification;
 - (ii) The experience of patient exposure to the product – e.g. sales volume, patient-years;
 - (iii) A summary of the product safety profile based on worldwide and local spontaneous adverse drug reaction reports, post-marketing surveillance data, clinical trials and published literature;
 - (iv) A list of the potential problems arising from using the product without medical supervision; and
 - (v) An analysis of the hazards arising from therapeutic misuse or drug abuse, whether deliberate or accidental e.g. consequence of delay in seeking medical attention.

25.3.1 'Me-too' Reclassification

The documentary requirements for a 'me-too' reclassification application include:

- (a) Section 1.1 – Comprehensive Table of Contents;
- (b) Section 1.2 – Introduction – including the justification for reclassification , as listed above, *and* the Table of Amendment Details of PRISM section 0.5;
- (c) Section 1.3 – PRISM Application Form;
- (d) Section 1.4 – Product Labels – the proposed product labels/PIL should also be submitted, if applicable; and
- (e) Section 1.5 – Approved SPC/PI/PIL, if applicable.

The Summary of Clinical Safety in Module 2/Part IV is not required.

CHAPTER H MINOR VARIATION (MIV) APPLICATION SUBMISSION

This chapter applies to minor variation applications for currently registered products.

26 APPLICATION TYPES

There are two types of minor variation application types:

MIV-1: A minor variation to the quality aspects, i.e. chemistry, manufacturing controls and/or product labelling.

MIV-2: A minor variation or an administrative change.

27 APPLICATION SUBMISSION

Applicants should be familiar with the guidelines and documentary requirements described in Appendix 13 (chemical) and Appendix 14 (biologics) before submitting minor variation applications.

There are two submission routes – abridged or verification route.

An application may be submitted via the verification route if:

- (i) The proposed variation(s) must be identical to those approved by one of HSA's reference agencies; and
- (ii) The application is accompanied by the proof of approval or approved product labels of that reference agency.

Applications that do not fulfil the above requirements should be submitted via the abridged route.

For details regarding PRISM submissions of variation applications, please refer to Appendix 17 *Guideline on PRISM Submission*. For target processing timelines for MIV-1 applications, please refer to Appendix 5 *Target Processing Timeline*

The following points should be considered when submitting an MIV:

- If one MIV contains multiple changes that belong to both MIV-1 and MIV-2 categories, then the MIV should be categorised as an MIV-1;
- MIV-1 changes should be grouped together as one application when these are consequential changes;
- Non-consequential MIV-1 changes are strictly not allowed. For instance, for a CMC MIV-1 application, MIV-1 updates to the product labelling unrelated to CMC changes will not be accepted;
- HSA reserves the right to split unrelated consequential changes into separate MIV application(s), if deemed necessary; and
- If a proposed MIV-2 does not meet its specified conditions, then the MIV must be categorised as an MIV-1 with supporting documents.

HSA may re-categorise the MIV if deemed appropriate.

NOTE: Applicants are encouraged to submit the *MIV Filing and Submission Enquiry Form* in Appendix 12 if there are any issues regarding the categorisation of variation applications.

Applicants should ensure that all conditions and documentary requirements for the MIV have been fulfilled prior to submission. For an MIV with multiple variations, all of the requirements for each individual variation must be met.

Applicants are strongly encouraged to submit variation applications for multiple strengths of the same therapeutic product at the same time. Applicants are also strongly encouraged to indicate in the PRISM application form and cover letter (to be attached under “Introduction” in PRISM) if the proposed change(s) affect multiple products and if there are other pending variation (MAV/MIV) applications for the same therapeutic product.

Any undisclosed variation(s) embedded in the submitted data, including any flow-on changes, will not be considered. Evaluation will be based on the data relevant to the proposed variation(s), unless HSA specifically requests for additional information.

It is the applicant's responsibility to ensure the completeness of the dossier and compliance with all specified requirements – failure to do so may delay the MIV review process.

No further changes to the application are allowed after acceptance in order to facilitate the timely processing of all applications, with the exception of HSA-initiated safety related changes.

For each product registration, applicants may submit up to a maximum of five concurrent MIV-1 applications and one MIV-2 application at any one time.

HEALTH SCIENCES AUTHORITY

Health Products Regulation Group
Blood Services Group
Applied Sciences Group

www.hsa.gov.sg

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